DENALI™

Discover, Develop, Defeat Degeneration

Ryan J. Watts, Ph.D., CEO

March 2018

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Accuracy of Data

This presentation contains statistical data based on independent industry publications or other publicly available information, as well as other information based on Denali's internal sources. We have not independently verified the accuracy or completeness of the data contained in these industry publications and other publicly available information. Accordingly, Denali makes no representations as to the accuracy or completeness of that data.

SUMMARY

Neurodegeneration

ONE OF THE BIGGEST UNMET MEDICAL NEEDS OF OUR TIME

- Alzheimer's, Parkinson's, ALS and other neurodegenerative diseases affect millions
- Few effective therapeutic options currently available

Time is Right

SCIENCE IS BREAKING OPEN

- Degenogenes enhance our understanding of disease biology and pathways
- Biomarkers enable identification of patients with the relevant disease biology

Our Approach

PRINCIPLES AND PARTNERSHIPS

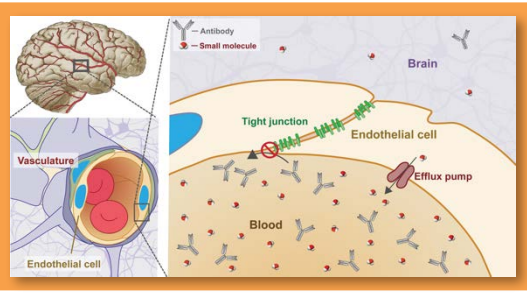
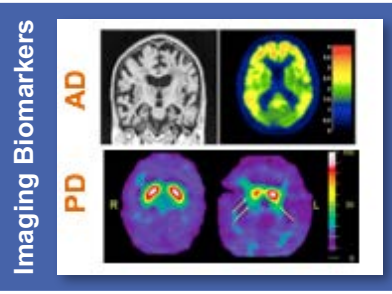
- Driven by three principles to increase probability of success
- Strategic collaborations to build, develop and commercialize broad portfolio

Our Pipeline

DIVERSIFIED AND DEEP EFFORT

- 7 core programs + 6 seed programs + discovery programs
- BBB platform technology to improve delivery of large molecules to brain
- 2018: Human target engagement for 2 programs, initiate patient studies

DE-RISKING DISCOVERY & DEVELOPMENT IN NEURODEGENERATION

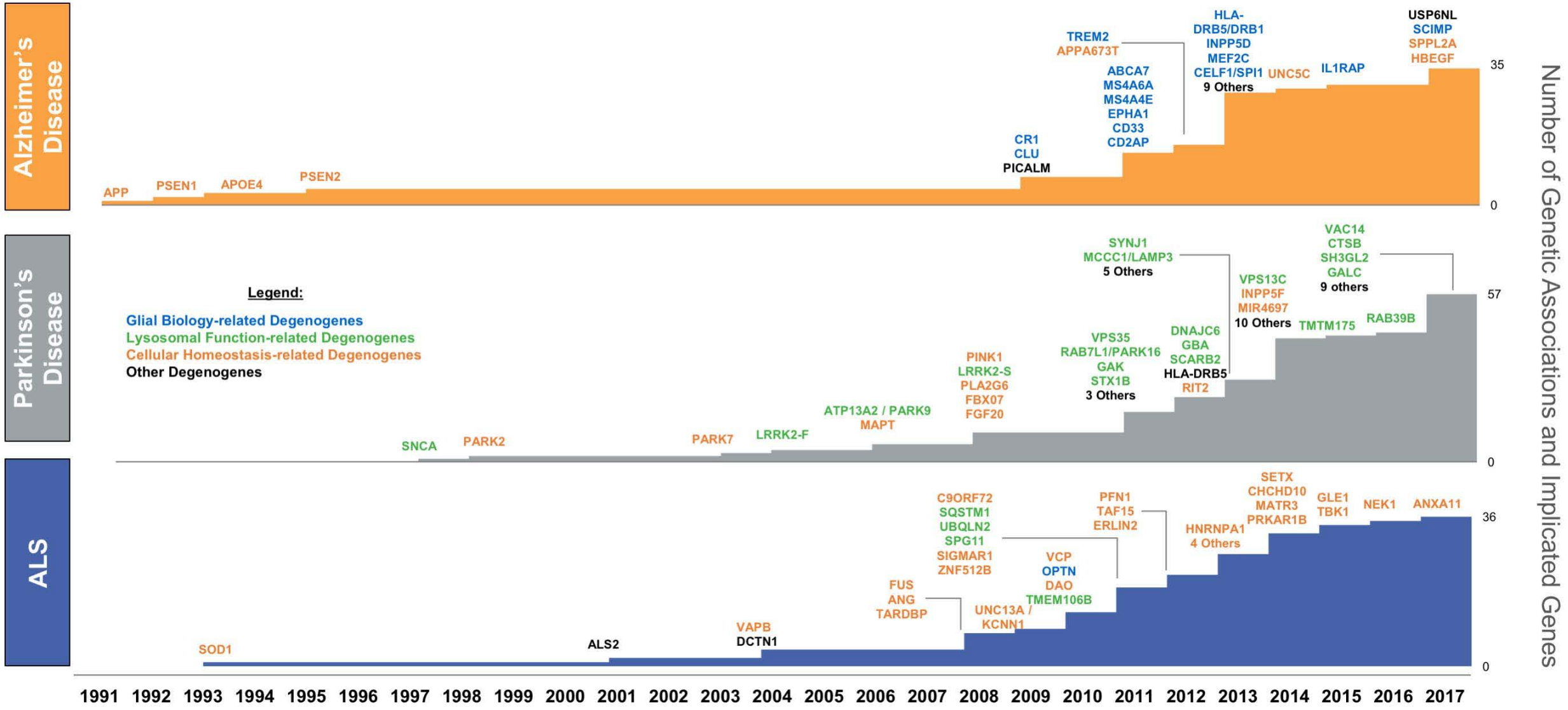
	Our Approach		Rationale
Genetic Pathway Potential	• Human genetics • Disease pathway focus		• Better targets • First-in-class molecules
Engineering Brain Delivery	• Engineering approach for small molecules • BBB platform for large molecules		• Improved brain penetration • Improved target engagement
Biomarker-Driven Development	• Targeted patient population • Target & pathway engagement		• The right patients • The right molecule • The right dose

Broad Portfolio | **Parallel Investment (lead and back-ups)** | **Strategic Partnering**

INCREASED PROBABILITY OF SUCCESS

DEGENOGENES DEFINE NEURODEGENERATION BIOLOGY

NEW GENETIC INSIGHTS IN ALZHEIMER'S, PARKINSON'S AND ALS

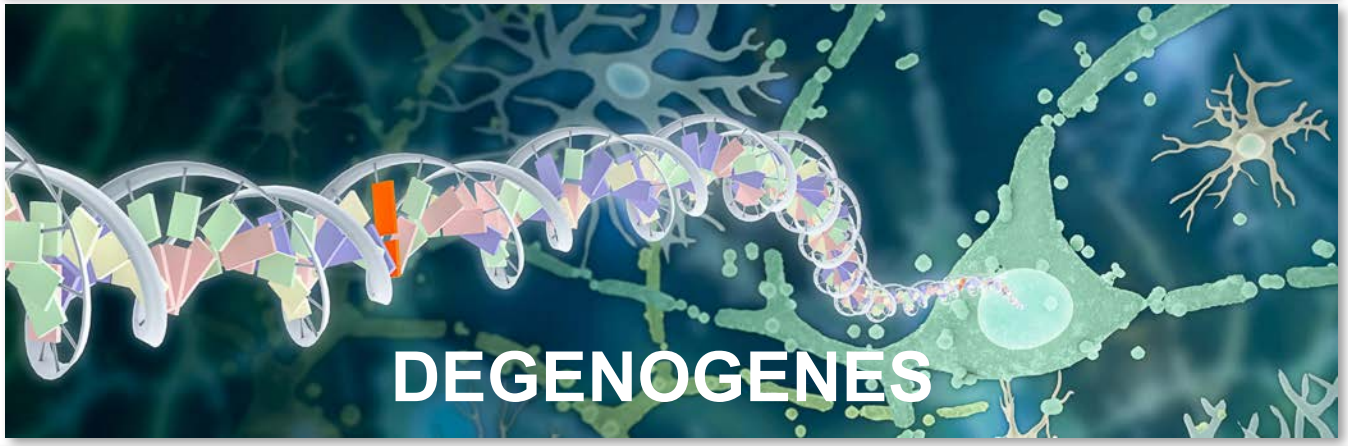


GENETIC PATHWAY POTENTIAL: BUILDING DEEP SCIENTIFIC INSIGHT

Indications

- Alzheimer's disease
- Parkinson's disease
- Amyotrophic Lateral Sclerosis
- Lysosomal Storage Diseases
- Huntington's disease
- Frontotemporal Dementia
- Multiple System Atrophy
- Other Diseases

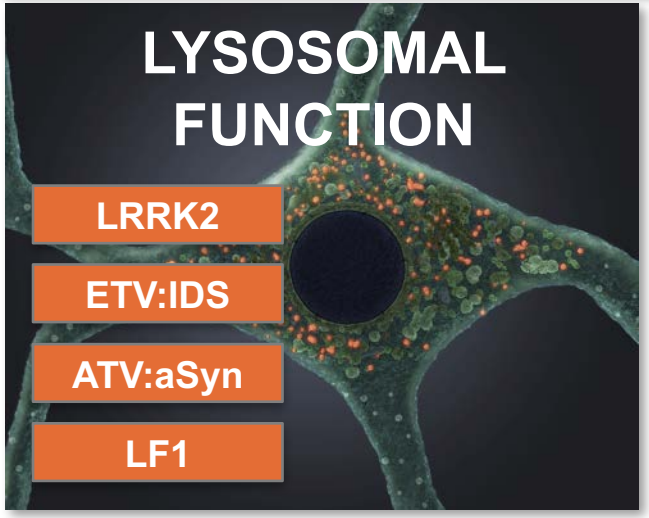
Human Genetics

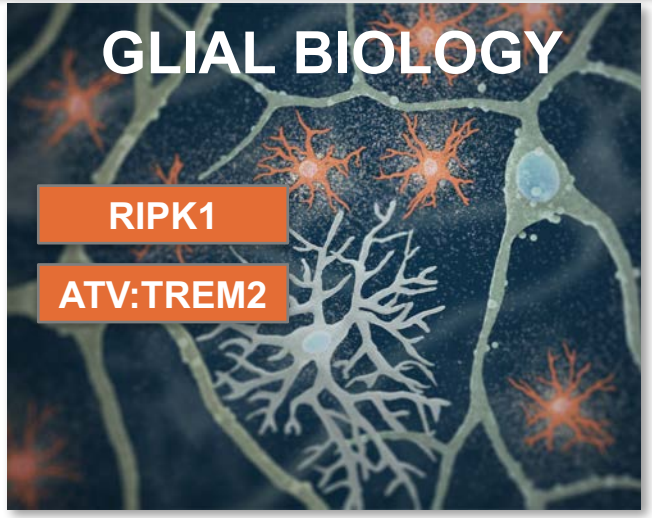


CORE (7)

SEED (6)

Pathways





DENALI PORTFOLIO – MARCH 2018

PROGRAM TARGET	DRUG CANDIDATE	THERAPEUTIC MODALITY	DISEASE INDICATION	DRUG DEVELOPMENT				VALIDATED BIOMARKER			PARTNERSHIP
				LEAD FINDING	LEAD OP	PRECLINICAL	PH 1	P	C	PS	
LYSOSOMAL FUNCTION PATHWAY											
LRRK2	DNL201	Small Molecule	Parkinson's Disease					✓	✓	✓	
	DNL151	Small Molecule	Parkinson's Disease					✓	✓	✓	
Alpha-Synuclein	ATV:aSyn	Antibody	Parkinson's Disease, DLB, MSA					✓			
Iduronate 2-sulfatase	ETV:IDS	Enzyme	MPS II (Hunter Syndrome)					✓	✓	✓	
LF1	LF1	Protein	Neurodegeneration					✓	✓	✓	Takeda
LF2	LF2	Small Molecule	Neurodegeneration					✓	✓	✓	
LF3	ETV:LF3	Enzyme	LSD					✓	✓	✓	
GLIAL BIOLOGY PATHWAY											
RIPK1	DNL747	Small Molecule	Alzheimer's Disease, ALS					✓	✓		
	DNL788	Small Molecule	Alzheimer's Disease, ALS					✓	✓		
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CH3	CH3	Small Molecule	Neurodegeneration					✓			
OTHER											
OP1	OP1	Small Molecule	TBD					✓	✓		

CORE program (7)

SEED program (6)

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P = Preclinical
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CH2	CH2	Antibody	Neurodegeneration							✓	
CH3	CH3	Small Molecule	Neurodegeneration					✓			
OTHER											
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SEED program (6)

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Glial Biology

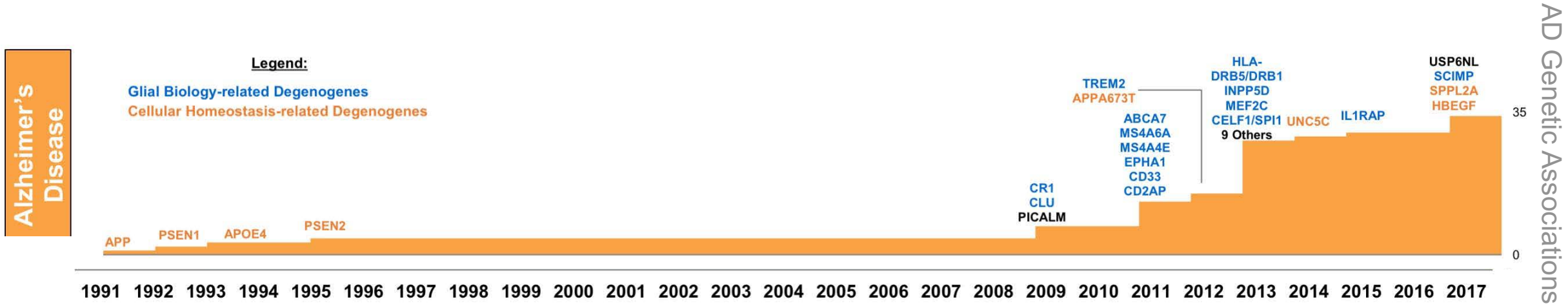
RIPK1i

ATV:TREM2

DEGENOGENES IMPLICATE GLIAL BIOLOGY (IMMUNE FUNCTION) IN AD

NEW GENETIC INSIGHTS IN ALZHEIMER'S DISEASE

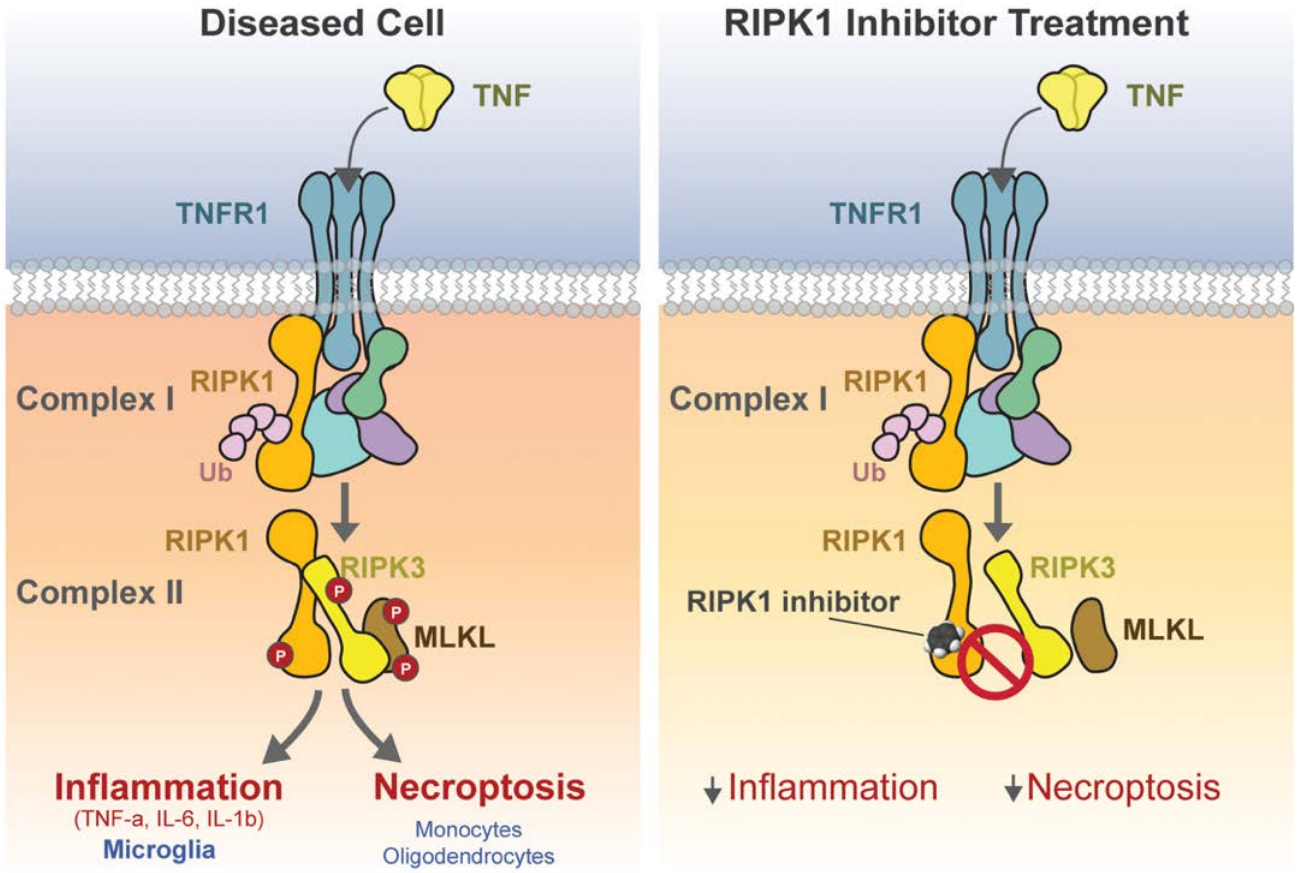
- Immune dysfunction is observed in patients with AD and other neurodegenerative diseases
- Degenogenes include TREM2 and numerous other genes that are highly expressed in inflamed microglia, the resident immune cells of the brain



- Neuro-immune modulation in neurodegeneration is a promising therapeutic approach
- RIPK1, a kinase downstream of the TNF receptor pathway, is overactive in inflamed microglia and several other cells in the brain

RIPK1 Inhibitor

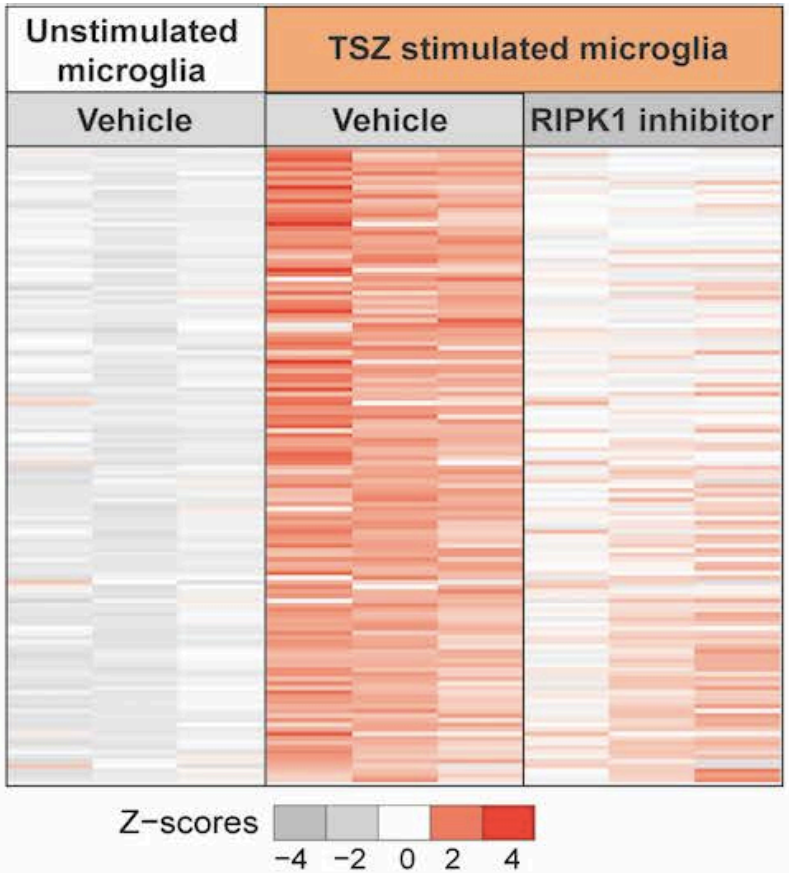
RIPK1 REGULATES INFLAMMATION AND NECROPTOSIS

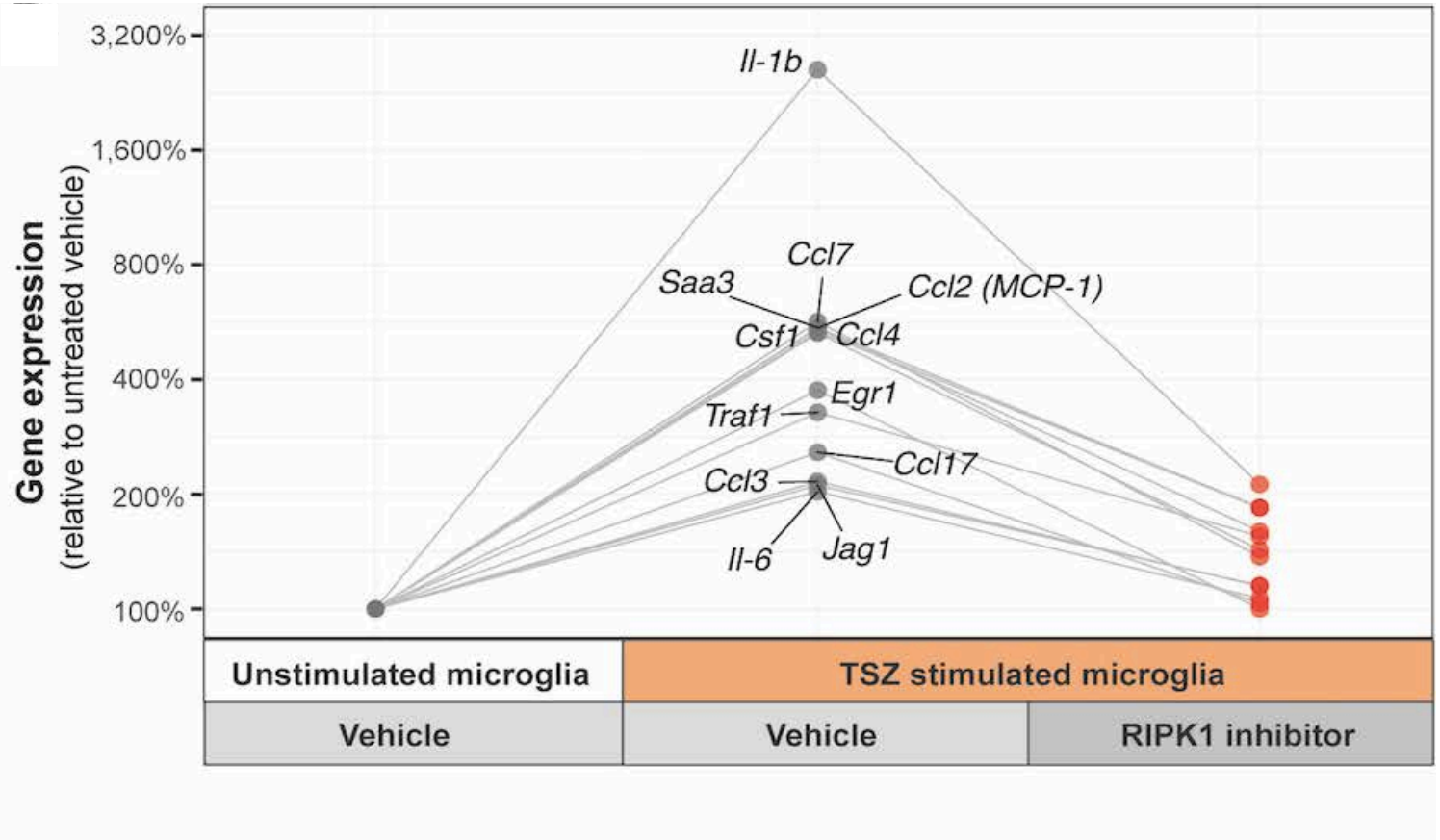


- Activation of RIPK1 kinase activity generates a pro-inflammatory response in microglia and cell death via necroptosis in other cell types, including monocytes and oligodendrocytes
- Inhibition of RIPK1 is sufficient to block both the production of pro-inflammatory cytokines and necroptosis

RIPK1 Inhibitor

RIPK1 INHIBITION BLOCKS INFLAMMATION IN HUMAN MICROGLIA



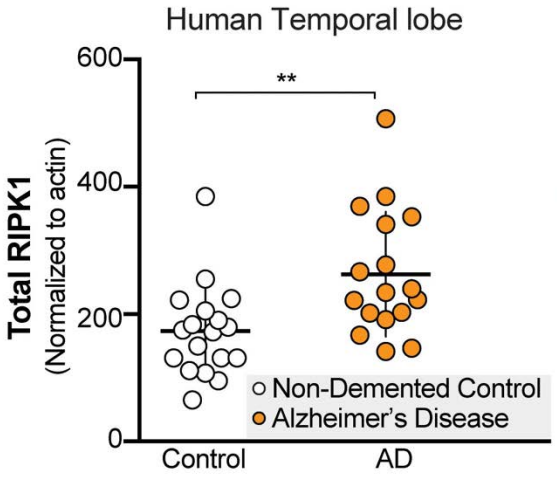


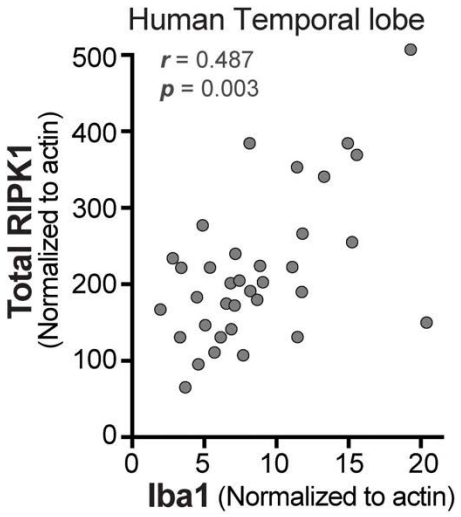
- Stimulation of microglia with a TNF cocktail (TSZ) results in induction of many genes, and the majority of these changes are reversed after treatment with a RIPK1 inhibitor
- Many of the top upregulated genes are pro-inflammatory cytokines and chemokines such as IL-1b, IL-6 and Ccl2 (MCP-1)
- Results suggest that production of pro-inflammatory cytokines in microglia is RIPK1 dependent

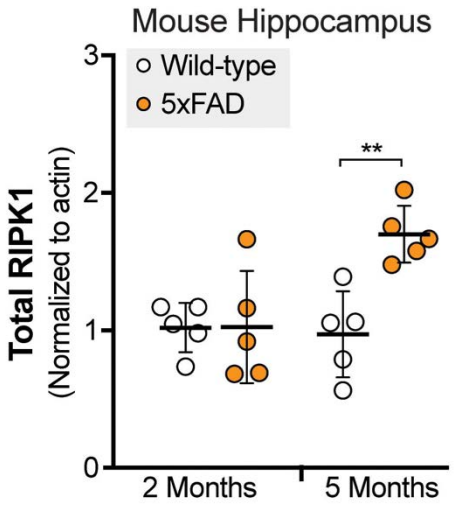
RIPK1 Inhibitor

RIPK1 IN ALZHEIMER'S DISEASE

RIPK1 increased in brains of human AD patients and in an Alzheimer's mouse model







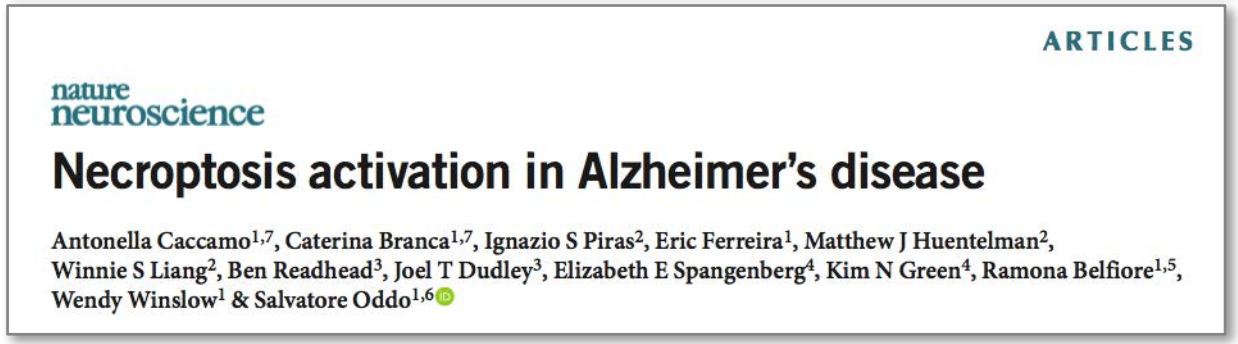
Denali Data

RIPK1 mediates a disease-associated microglial response in Alzheimer's disease

Dimitry Ofengeim[a,1], Sonia Mazzitelli[a,1], Yasushi Ito[a], Judy Park DeWitt[a], Lauren Mifflin[a], Chengyu Zou[a], Sudeshna Das[b,c], Xian Adiconis[d], Hongbo Chen[a], Hong Zhu[a], Michelle A. Kelliher[e], Joshua Z. Levin[d], and Junying Yuan[a,2]

[a]Department of Cell Biology, Harvard Medical School, Boston, MA 02115; [b]MassGeneral Institute for Neurodegenerative Disease, Massachusetts General Hospital, Cambridge, MA 02139; [c]Department of Neurology, Harvard Medical School, Boston, MA 02115; [d]Broad Institute, Cambridge, MA 02142; and [e]Department of Cancer Biology, University of Massachusetts Medical School, Worcester, MA 01605

Contributed by Junying Yuan, August 15, 2017 (sent for review August 11, 2017; reviewed by J. Marie Hardwick and David Rubinsztein)



ARTICLES

nature neuroscience

Necroptosis activation in Alzheimer's disease

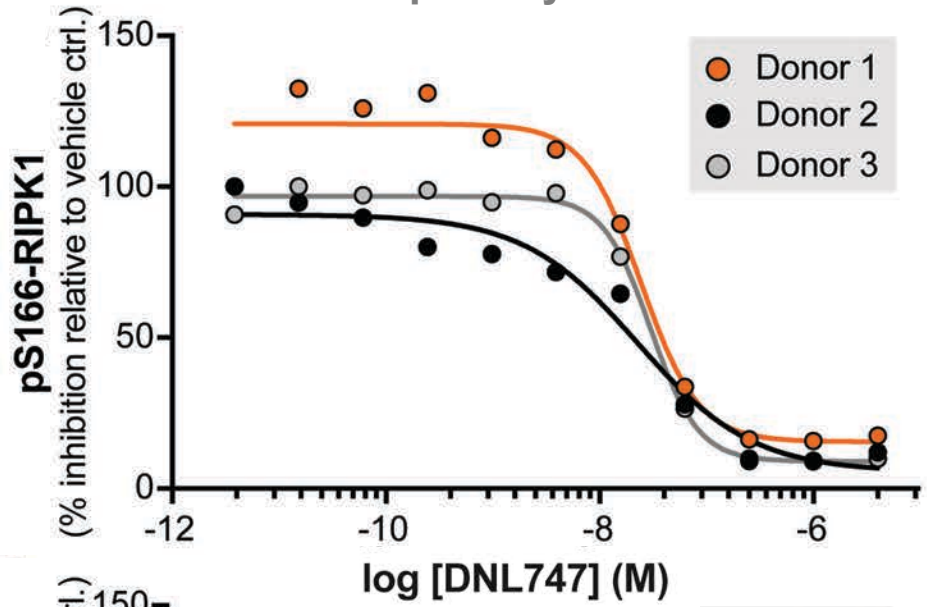
Antonella Caccamo[1,7], Caterina Branca[1,7], Ignazio S Piras[2], Eric Ferreira[1], Matthew J Huentelman[2], Winnie S Liang[2], Ben Readhead[3], Joel T Dudley[3], Elizabeth E Spangenberg[4], Kim N Green[4], Ramona Belfiore[1,5], Wendy Winslow[1] & Salvatore Oddo[1,6]

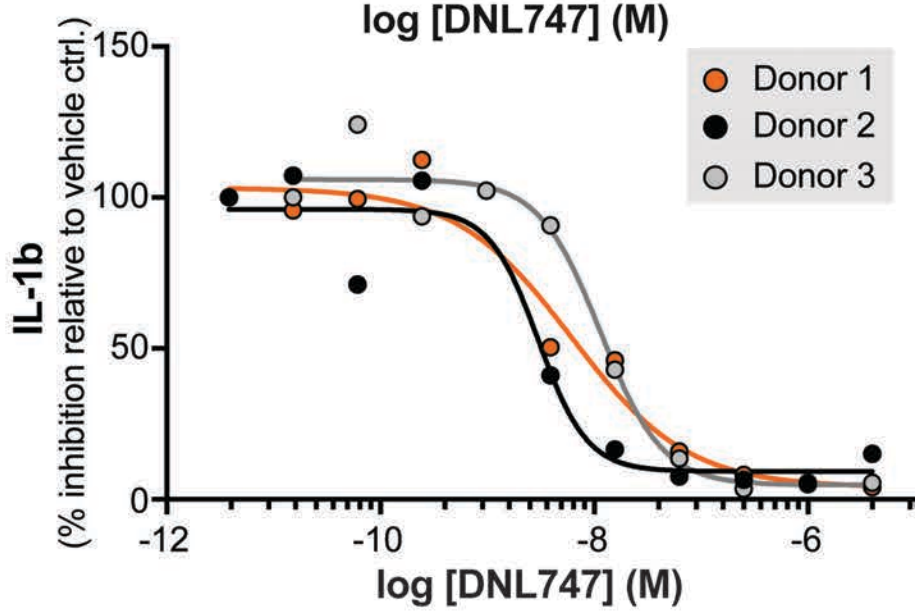
- RIPK1 pathway is activated in human AD patient brain and AD mouse models – *Denali data*
- Published literature shows protection in AD models with RIPK1 loss-of-function
- Clinical strategy: demonstrate peripheral target engagement in Ph1 healthy volunteer study; demonstrate central target engagement in a Ph2a biomarker study in AD patients

RIPK1 Inhibitor

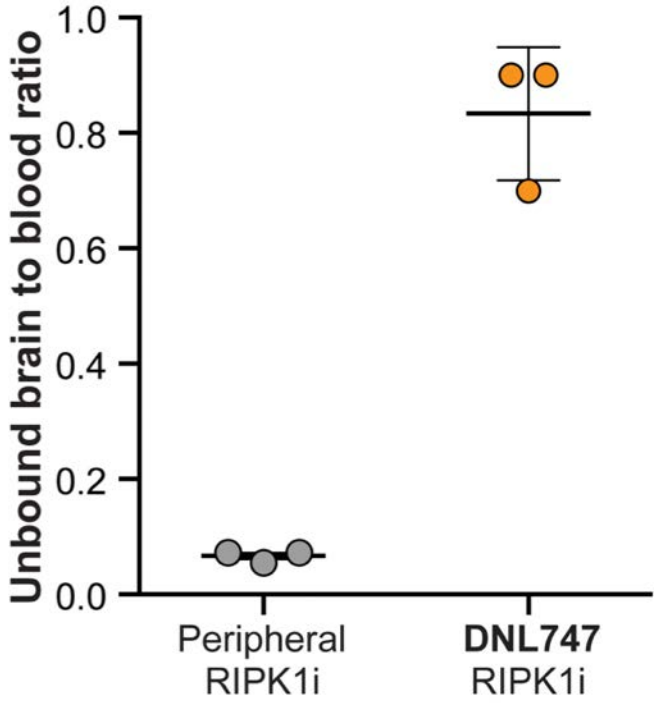
DNL747 PHARMACOLOGICAL PROPERTIES & BRAIN EXPOSURE

Treatment of primary human cells





Robust brain uptake with DNL747



- Treatment of primary human cells with DNL747 results in a dose dependent reduction in p-RIPK1 and IL-1b
- DNL747 show a brain to blood ratio of ~0.8 while a benchmark periphery-restricted RIPK1 inhibitor displays a ratio of ~0.05
- **CTA Filing for DNL747 planned for early 2018**

RIPK1 Inhibitor

DENALI PORTFOLIO – MARCH 2018

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LYSOSOMAL FUNCTION PATHWAY											
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CELLULAR HOMEOSTASIS											
BACE1/Tau	ATV:BACE1/Tau	Antibody	Alzheimer's Disease					✓	✓	✓	Takeda
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CH2	CH2	Antibody	Neurodegeneration							✓	
CH3	CH3	Small Molecule	Neurodegeneration					✓			
OTHER											
OP1	OP1	Small Molecule	TBD					✓	✓		

CORE program (7)

SEED program (6)

VALIDATED BIOMARKER
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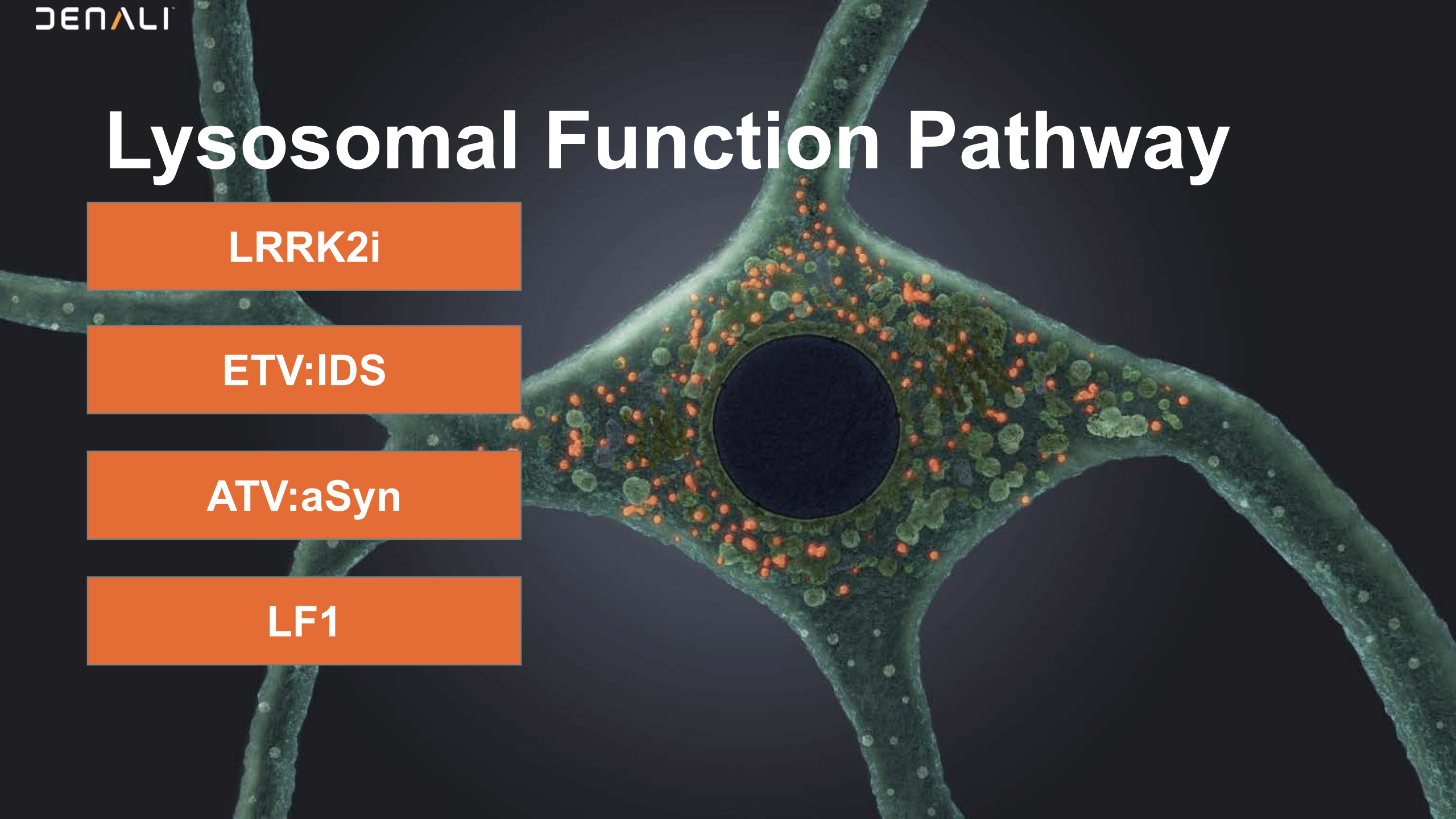
Lysosomal Function Pathway

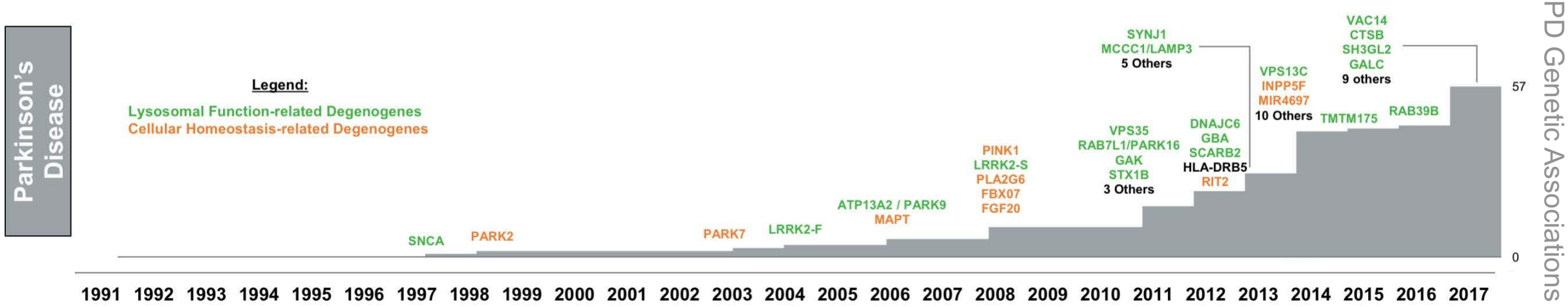


- LRRK2i
- ETV:IDS
- ATV:aSyn
- LF1

DEGENOGENES IMPLICATE LYSOSOMAL FUNCTION IN PD

NEW GENETIC INSIGHTS IN PARKINSON'S DISEASE

- Lysosomal dysfunction is a central pathophysiology of PD
- Parkinson's genetic risks highlight lysosomal impairment in PD
  - Lysosomal enzymes, GALC and GBA, are major risk factors for PD

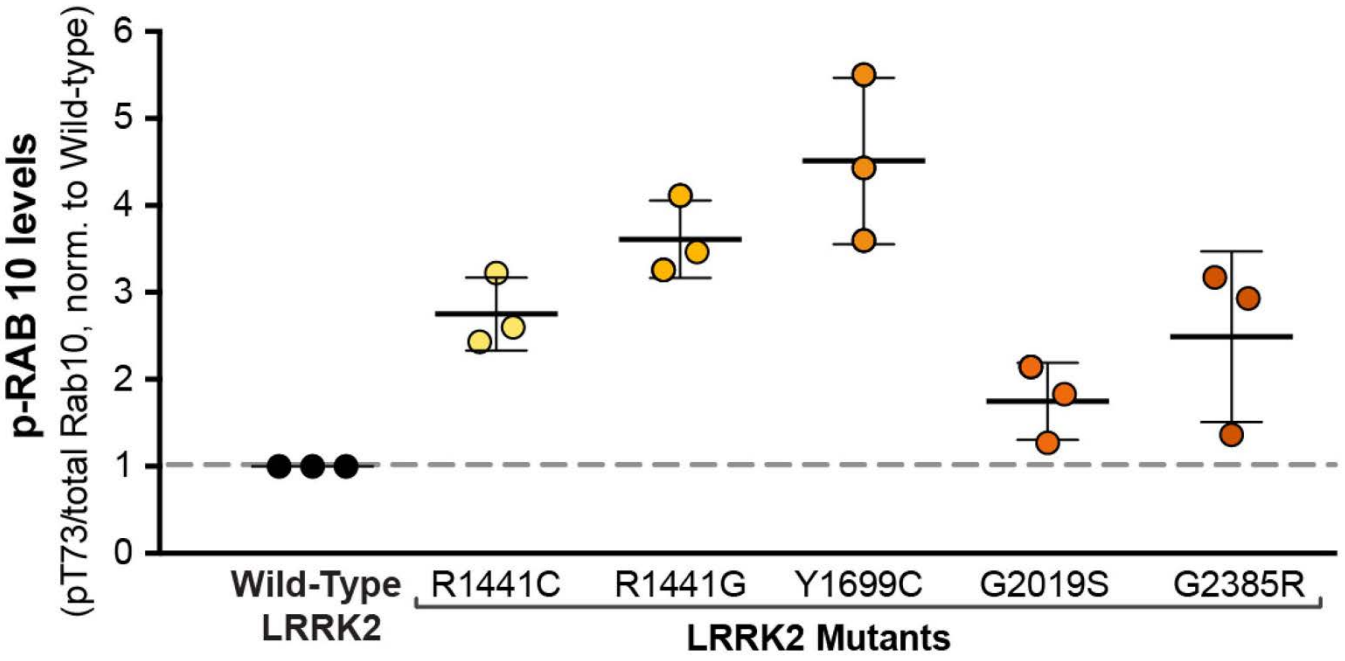


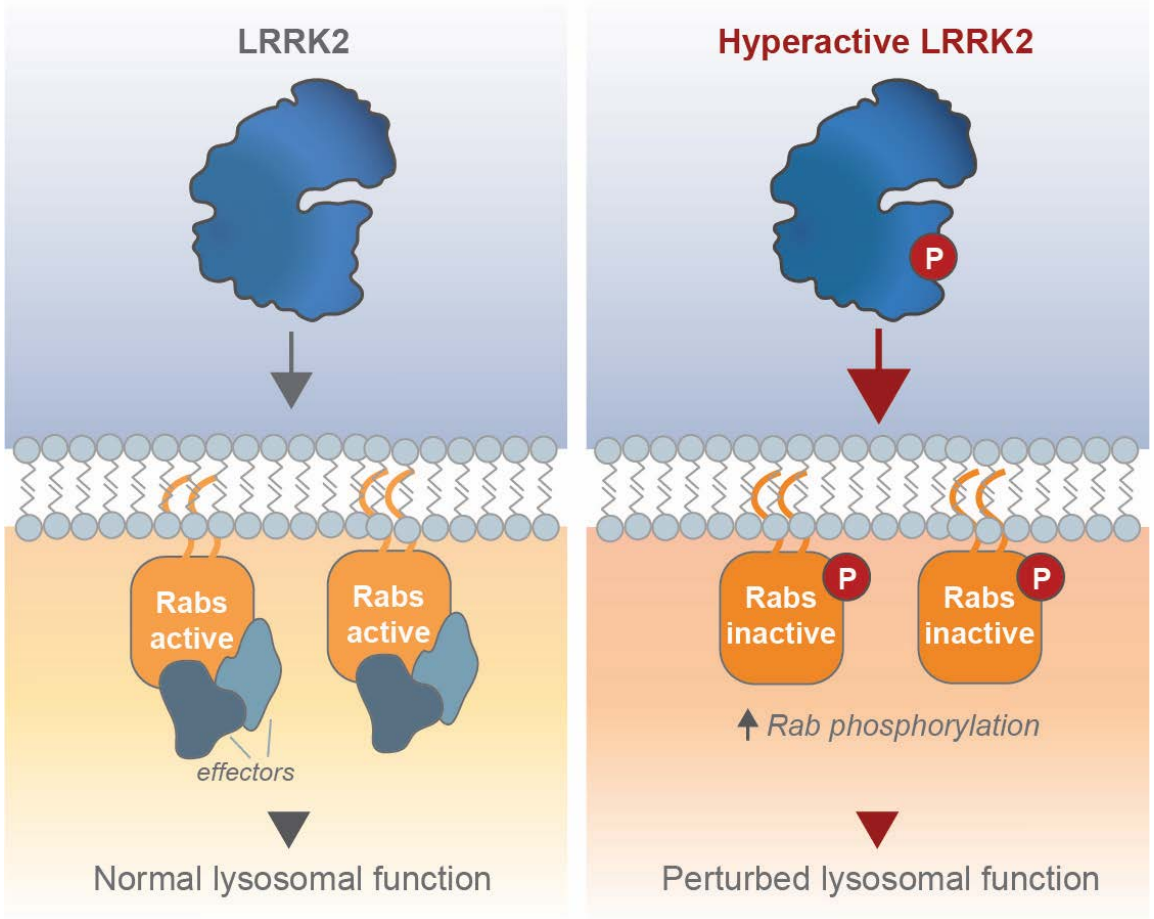
- Lysosomal dysfunction contributes to aSyn aggregation, the pathologic hallmark of PD
- LRRK2 and aSyn are linked to lysosomal function, and represent promising therapeutic targets

LRRK2 Inhibitor

LRRK2 DISEASE CAUSING MUTATIONS INCREASE KINASE ACTIVITY

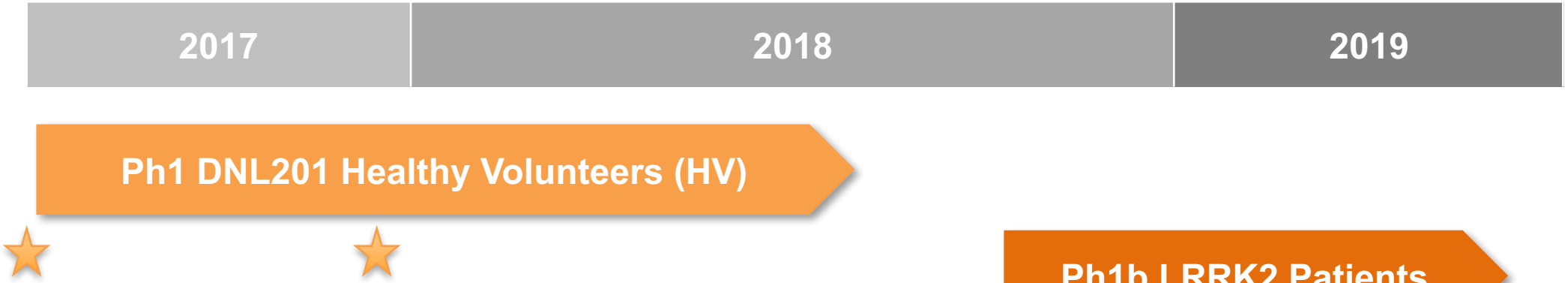
LRRK2 Parkinson's mutations increase pRab





LRRK2 Inhibitor

LRRK2 CLINICAL PROGRAM SUMMARY



- Ph1 initiated for DNL201

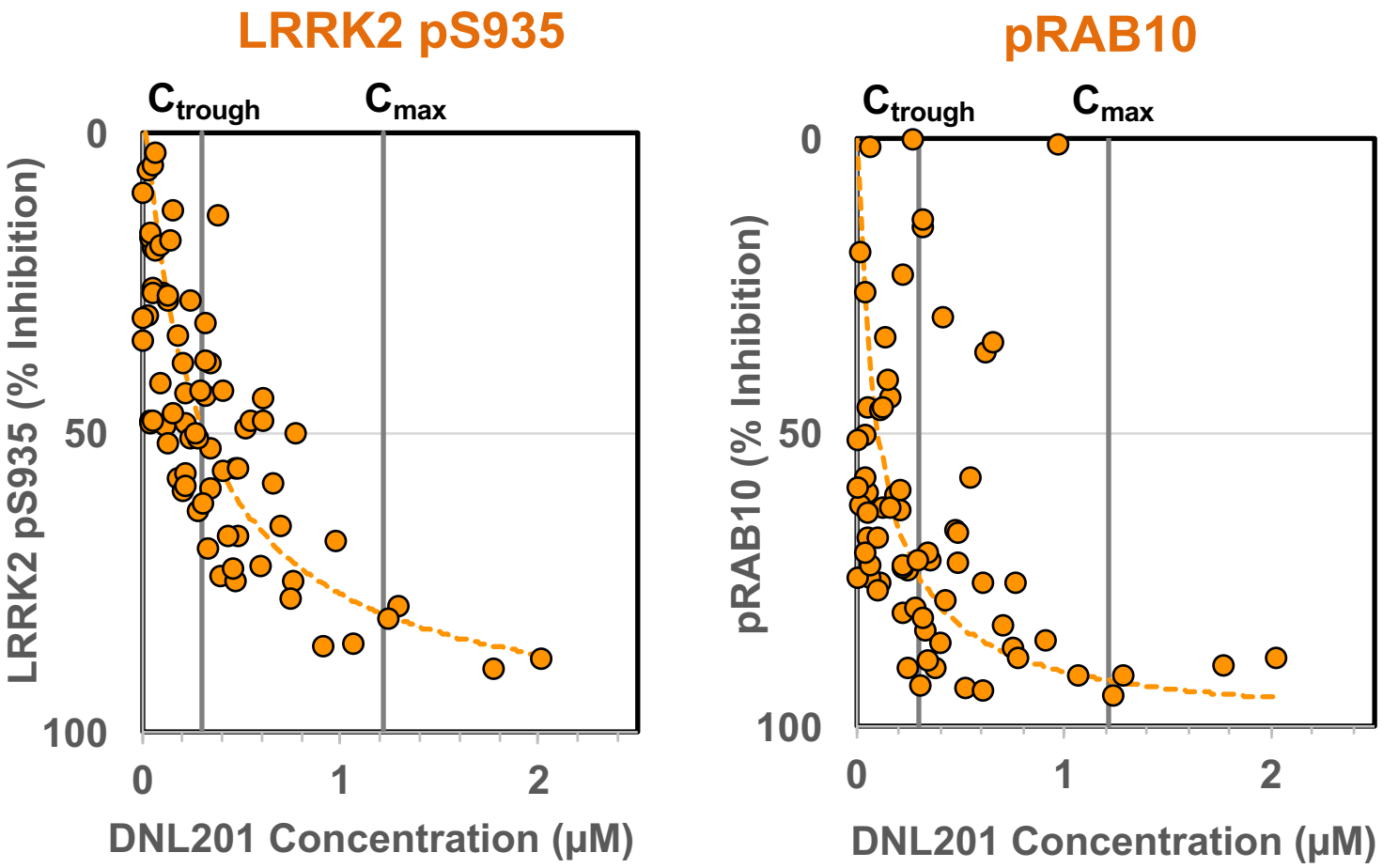
- **Target engagement achieved for DNL201**
- Partial clinical hold lifted
- Ph1 initiated for DNL151

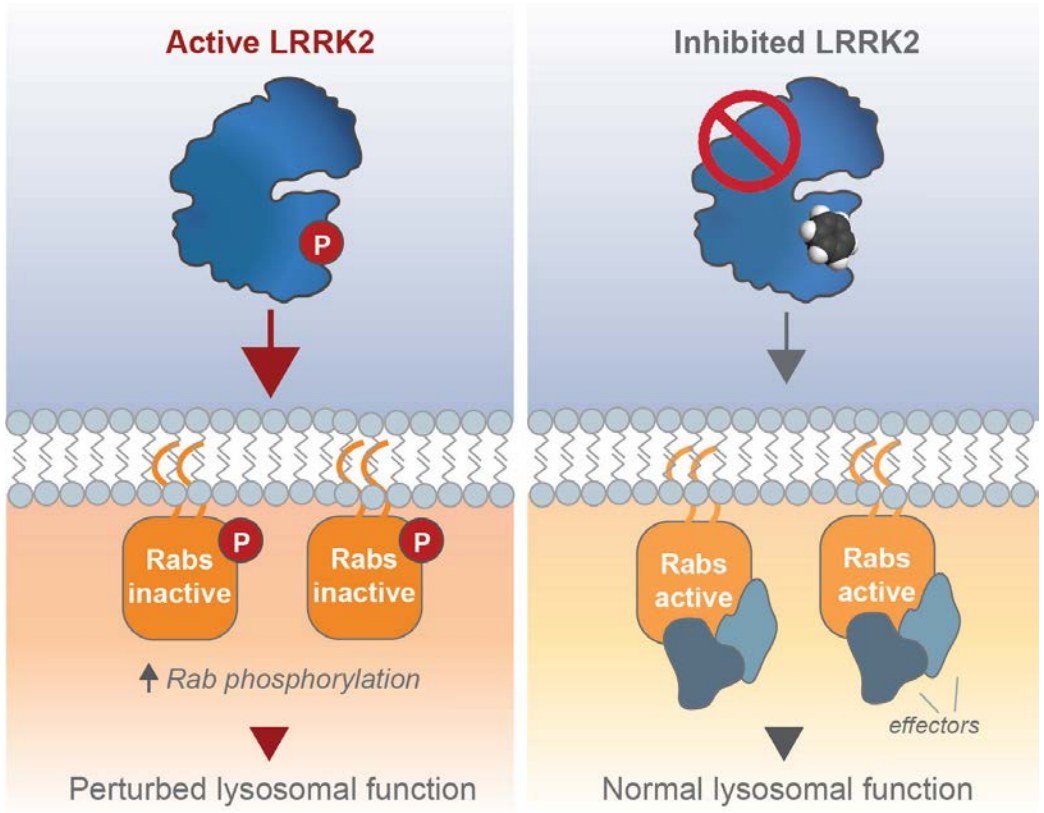
- Safety and PK/PD profile will determine advancement to Ph1b

- Phase 1b safety and biomarker data in LRRK2 Parkinson's patients

LRRK2 Inhibitor

PK/PD CORRELATION IN HUMANS DOSED WITH DNL201

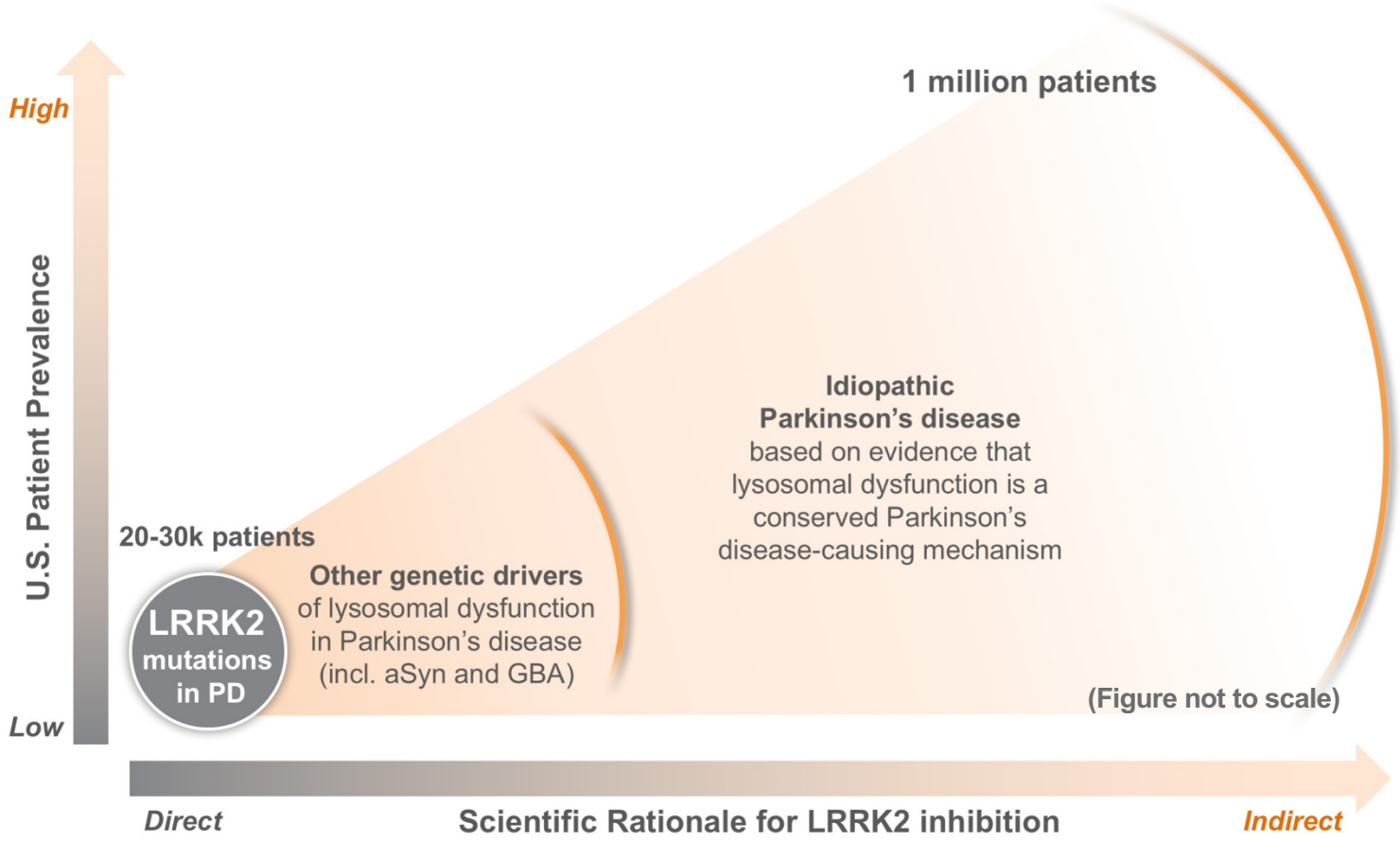




- Each point represents measured exposures from all active subjects at all time points on Day 1 and 10
- Concentration dependent inhibition and target engagement
- Mean greater than 50% and 90% inhibition of LRRK2 kinase activity observed at trough and peak drug levels, respectively

LRRK2 Inhibitor

LRRK2 INHIBITION HAS BROAD THERAPEUTIC POTENTIAL FOR PD



- Lysosomal dysfunction is a central pathophysiology of PD in patients with and without known genetic drivers of PD
- Inhibition of LRRK2 may be a therapeutically beneficial approach for many forms of PD

LRRK2 Inhibitor

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	DNL151	Small Molecule	Parkinson's Disease					✓	✓	✓	
Alpha-Synuclein	ATV:aSyn	Antibody	Parkinson's Disease, DLB, MSA					✓			
Iduronate 2-sulfatase	ETV:IDS	Enzyme	MPS II (Hunter Syndrome)					✓	✓	✓	
LF1	LF1	Protein	Neurodegeneration					✓	✓	✓	Takeda
LF2	LF2	Small Molecule	Neurodegeneration					✓	✓	✓	
LF3	ETV:LF3	Enzyme	LSD					✓	✓	✓	
GLIAL BIOLOGY PATHWAY											
RIPK1	DNL747	Small Molecule	Alzheimer's Disease, ALS					✓	✓		
	DNL788	Small Molecule	Alzheimer's Disease, ALS					✓	✓		
TREM2	ATV:TREM2	Antibody	Alzheimer's Disease					✓			Takeda
CELLULAR HOMEOSTASIS											
BACE1/Tau	ATV:BACE1/Tau	Antibody	Alzheimer's Disease					✓	✓	✓	Takeda
CH1	CH1	Small Molecule	Neurodegeneration					✓			
CH2	CH2	Antibody	Neurodegeneration							✓	
CH3	CH3	Small Molecule	Neurodegeneration					✓			
OTHER											
OP1	OP1	Small Molecule	TBD					✓	✓		

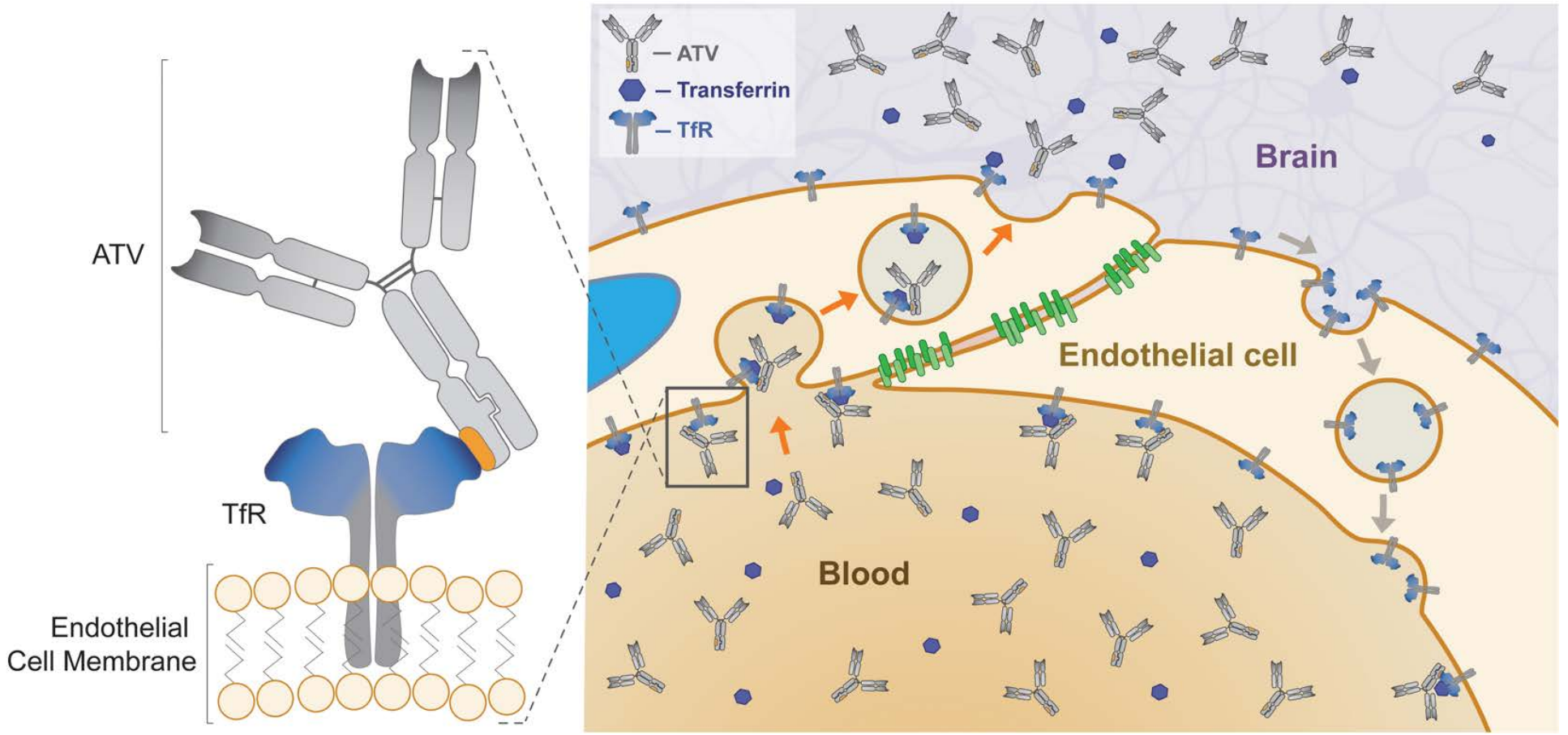
CORE program (7)

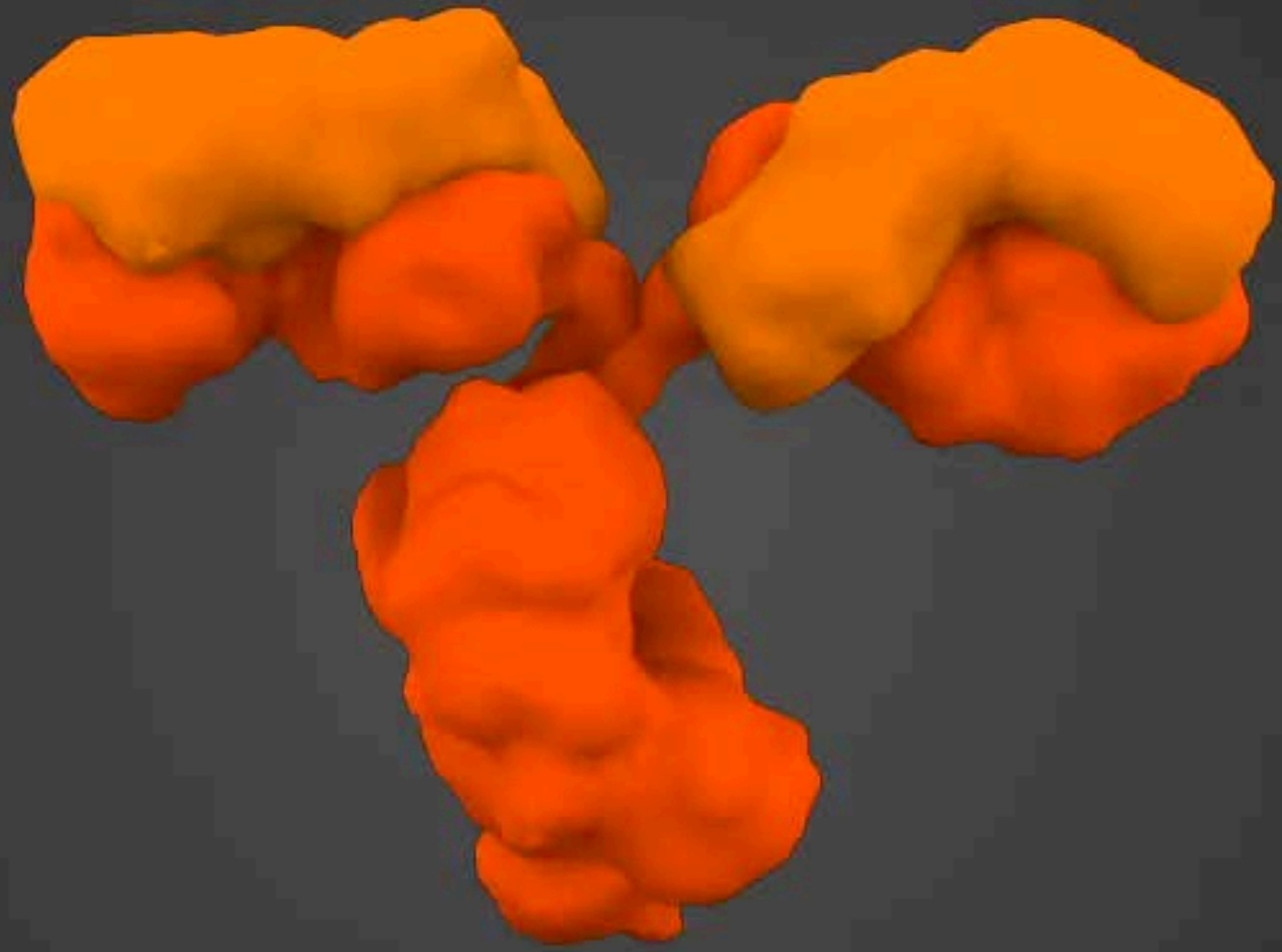
SEED program (6)

VALIDATED BIOMARKER
P = Preclinical
C = Clinical
PS = Patient Selection

ENGINEERING BRAIN DELIVERY: ANTIBODY TRANSPORT VEHICLE

- ATVs bind to Transferrin receptors on endothelial cells of the BBB
- TfR/ATV complexes are endocytosed and transported through the BBB
- ATV dissociates from TfR in the endosome and is released into the brain parenchyma

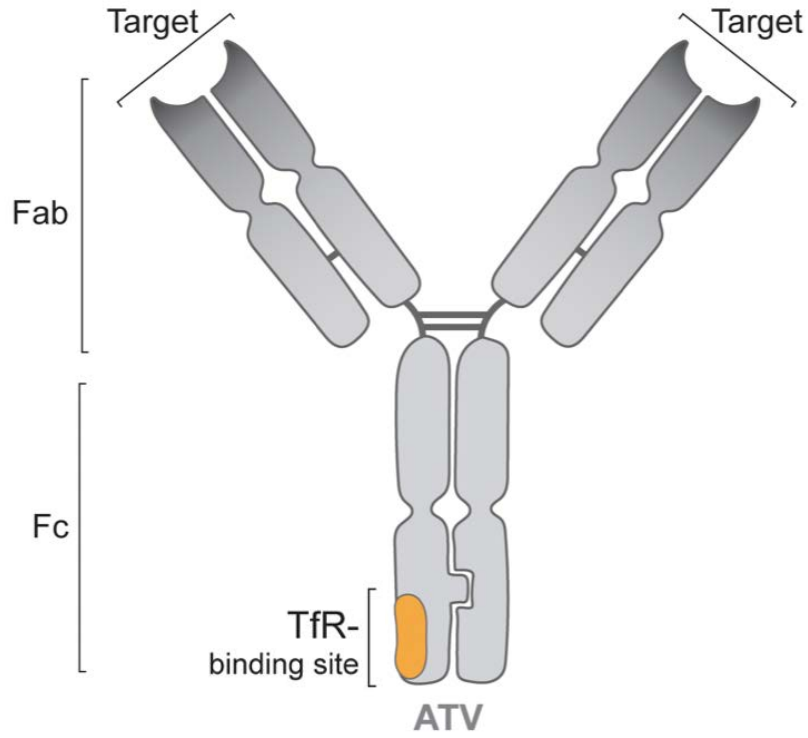




ANTIBODY TRANSPORT VEHICLE: ENGINEERING THE Fc TO BIND TfR

ATV is well differentiated from other BBB approaches

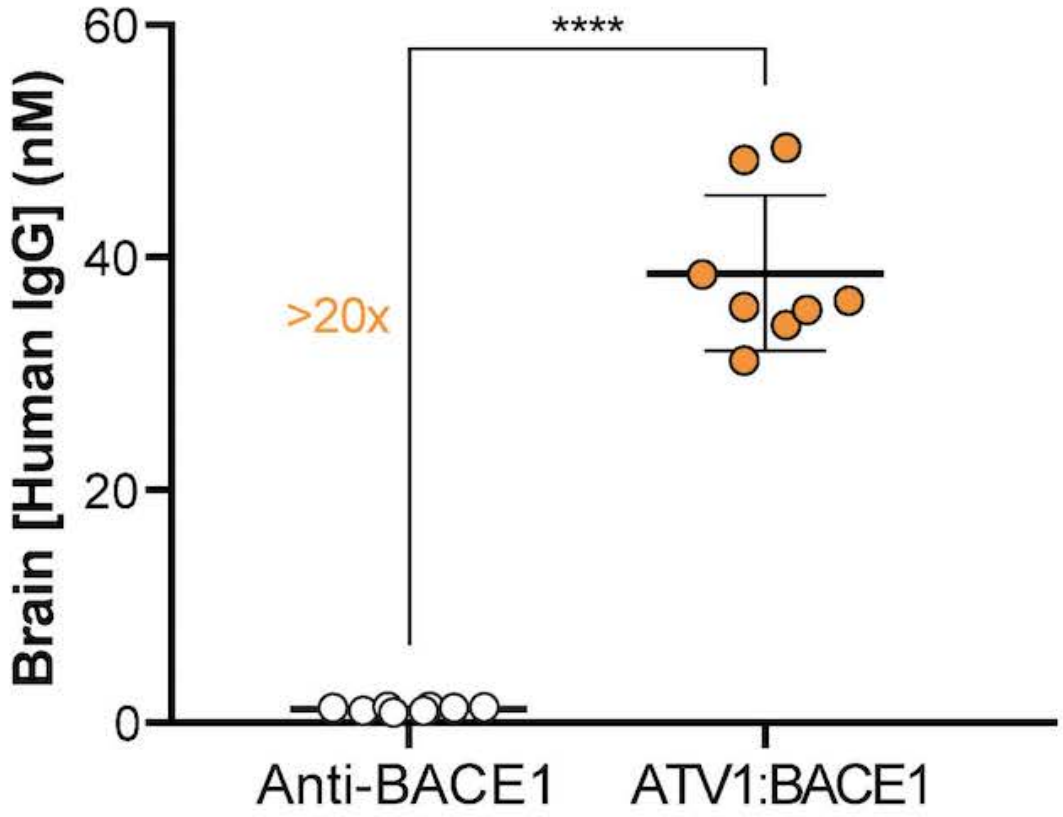
- Integrates BBB target binding site into IgG format
- No need for unnatural linkers or appended sequences
- Antibody-like **stability** and **pharmacokinetic** properties
- **Bivalent** or **bispecific** target binding enabled
- Initial *in vivo* proof of concept data in hu/ms TfR KI mouse and monkey



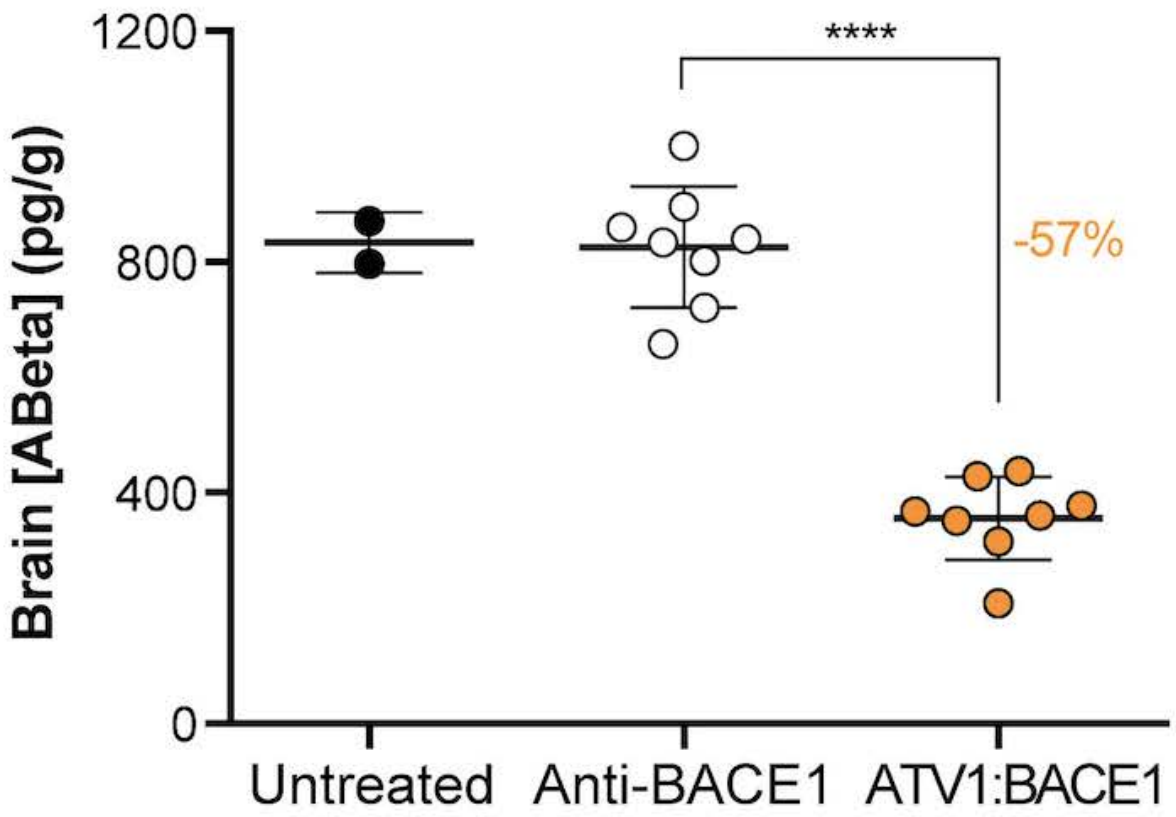
ATV = Antibody Transport Vehicle
BBB = blood-brain barrier
hu = human
ms = mouse
TfR = Transferrin Receptor
KI = knock-in

ROBUST BRAIN UPTAKE AND ACTIVITY IN HU/MS TfR MOUSE

PK: drug concentration in brain



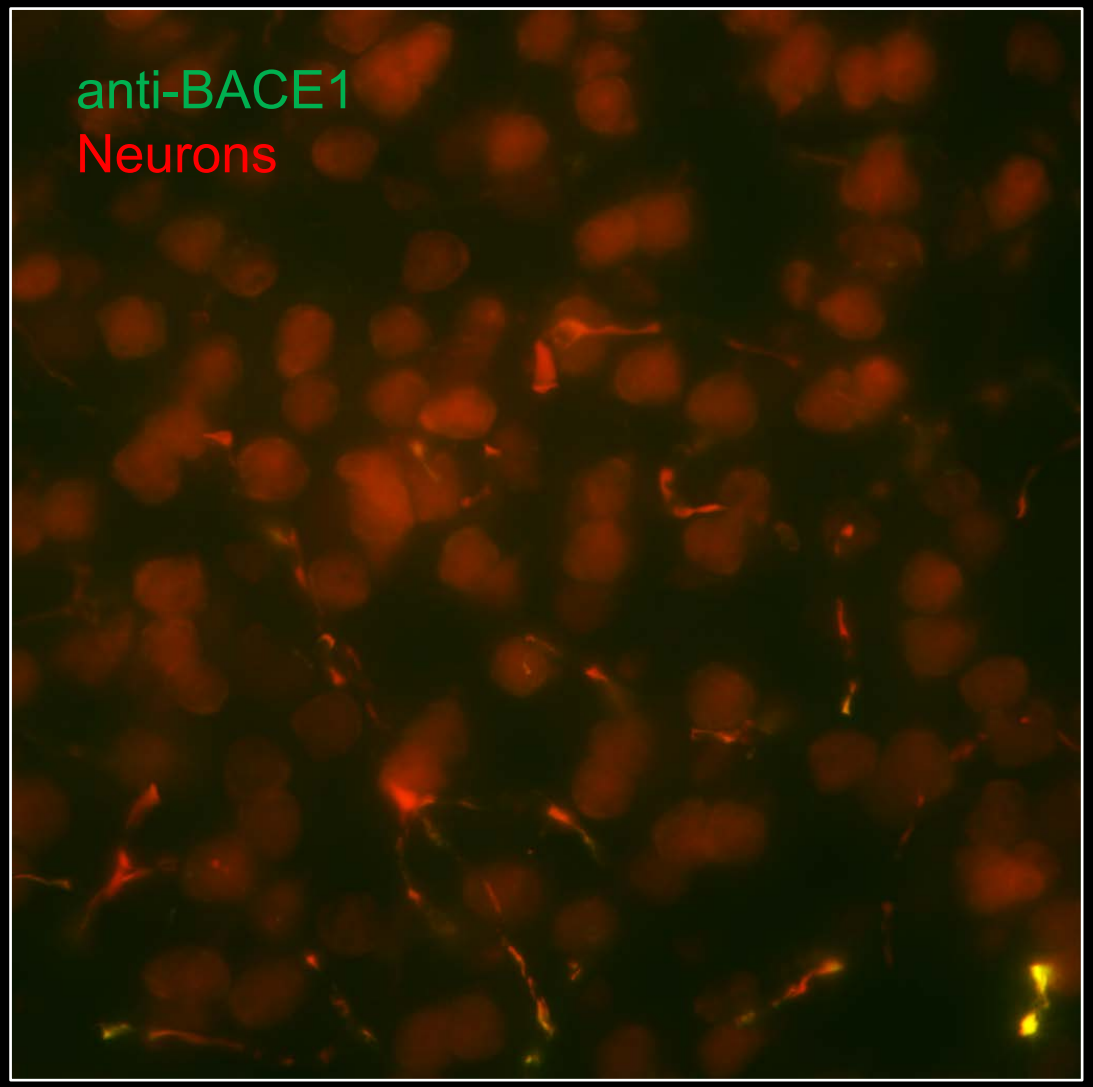
PD: Abeta reduction in brain

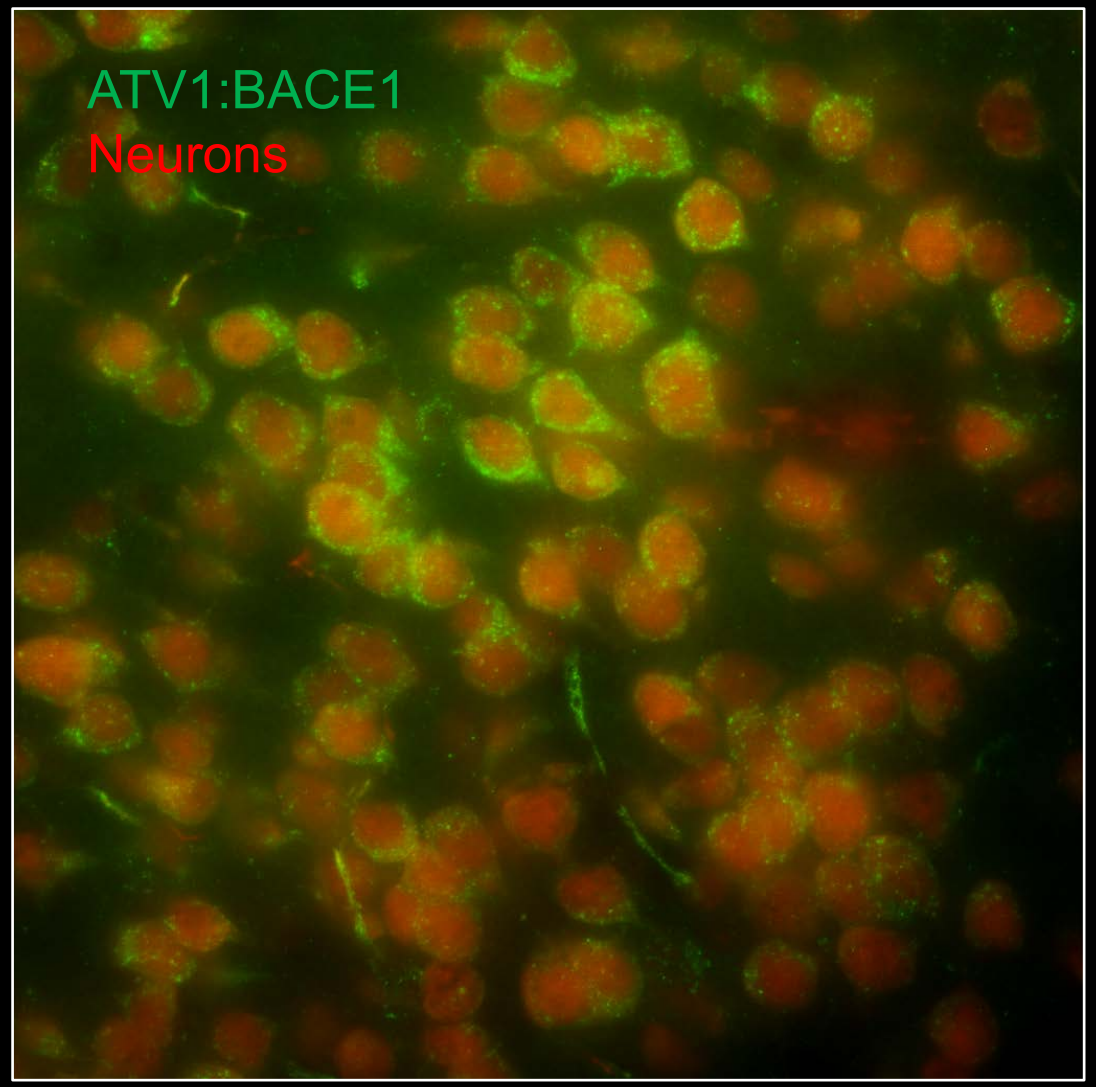


- 50 mg/kg IV dose in $TfR^{hu/ms}$ KI mice – 24 hour

BROAD DISTRIBUTION OF ATV IN BRAIN

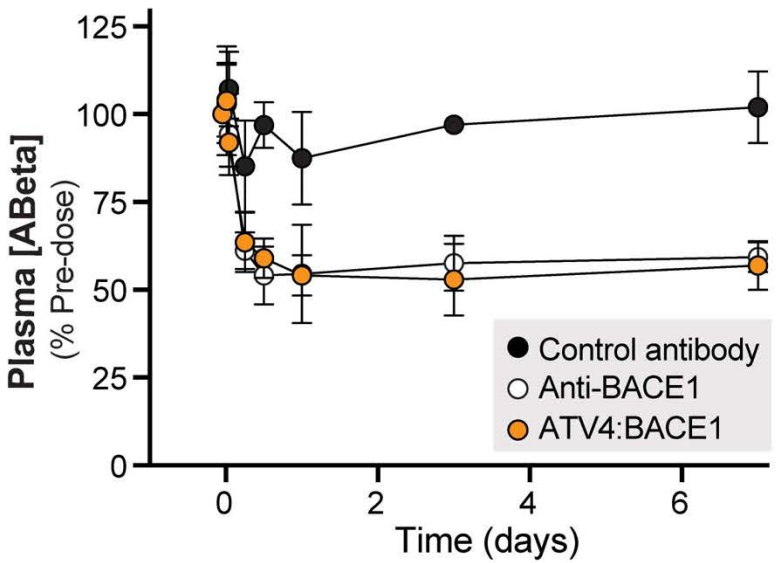
Localization of antibody in $TfR^{hu/ms}$ KI brain cortex 24hrs after 50 mg/kg IV

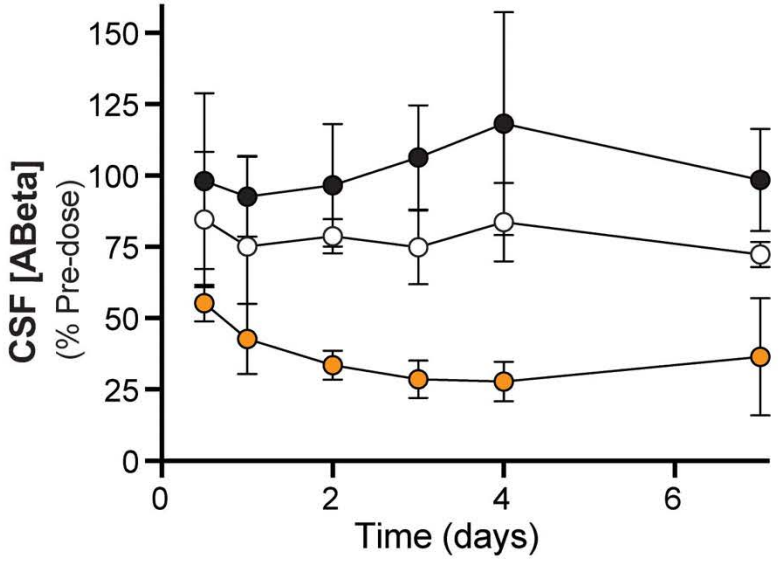


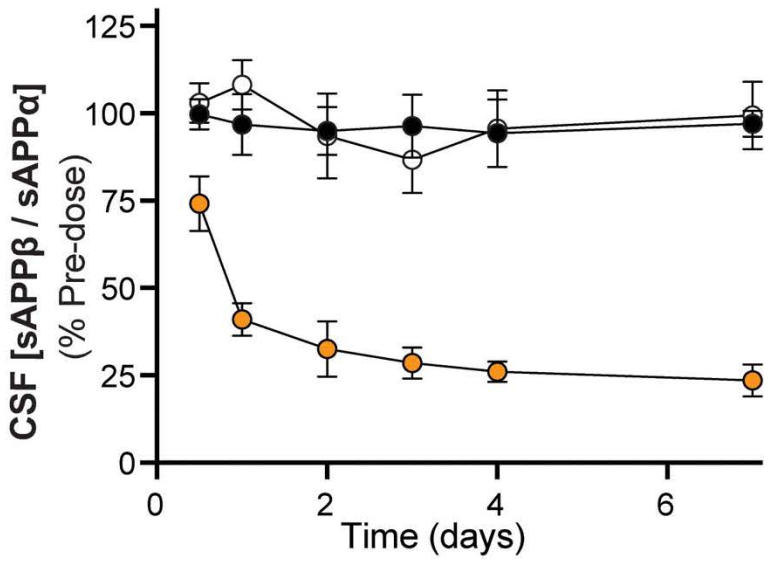


SUSTAINED PHARMACODYNAMIC RESPONSE IN NONHUMAN PRIMATES

PD: Abeta and sAPPbeta reduction in CSF taken from living monkeys (translatable biomarker)



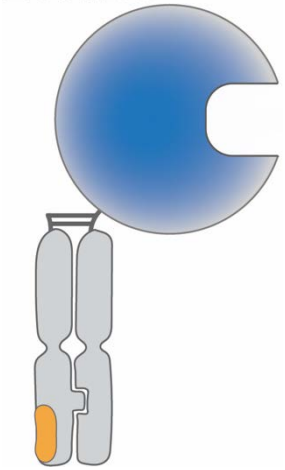




- 30 mg/kg single IV dose in cynomolgus monkey – time course

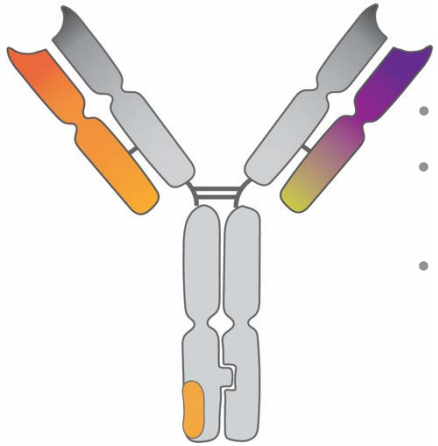
LARGE MOLECULE TARGETS: ATV AND ETV PLATFORM PORTFOLIO

ETV:IDS



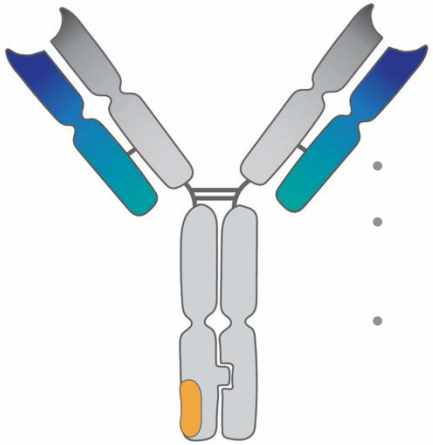
- Indication: **Hunter Syndrome**
- Status: *in vitro* and *in vivo* activity, candidate selected
- IND or CTA filing planned in 2019

ATV:BACE1/Tau



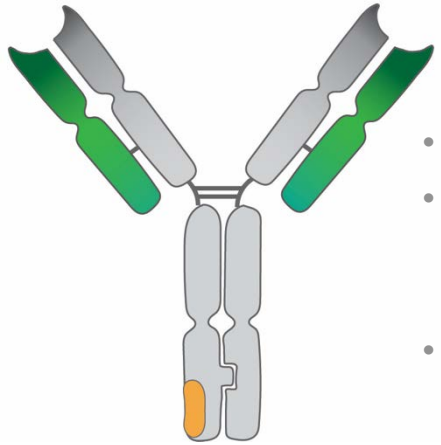
- Indication: **Alzheimer's disease**
- Status: high affinity, humanized leads for BACE1 & Tau
- IND or CTA filing planned in 2020

ATV:aSyn



- Indication: **Parkinson's disease**
- Status: multiple lead antibodies identified with robust binding to human CSF derived aSyn
- IND or CTA filing planned in 2020

ATV:TREM2



- Indication: **Alzheimer's disease**
- Status: high affinity candidate antibodies with diverse properties
  - Shedding blockers and agonist antibodies
- IND or CTA filing planned in 2020

PARTNERING IS CENTRAL TO OUR STRATEGY

- Network of current and former collaborators in academia and industry to build broad portfolio and deepen scientific expertise
- Continuing to explore partnering options with global biopharma companies for co-development and co-commercialization

STRATEGIC PARTNERSHIP WITH TAKEDA

Rationale

- Share development risk and commercial returns on early stage assets for large indications
- Enables Denali's broad portfolio approach and ability to fully explore potential of BBB technology
- Leverages Takeda's strong clinical development and global commercial capabilities

Scope (3 Named Programs)

- ATV:BACE1/Tau (IND estimated during 2020)
- ATV:TREM2 (IND estimated during 2020)
- Additional named (but undisclosed) discovery stage program (IND estimated post 2020)

Roles and Responsibilities

- Denali responsible for all pre-IND R&D activities
- Post opt-in (at IND), Denali will lead early clinical development and Takeda late stage development
- Co-commercialization in US and China; Takeda will commercialize in all other countries

Key Financial Terms (to Denali)

- $150M upfront payments between cash and equity*
- Up to $90M in pre-clinical milestones and opt-in payments, total deal value up to >$1.1B
- 50% of world wide commercial profits

*** Upfront payment includes purchase of approx. 4.2 million shares (~4.5% of DNLI equity) at $26.10/sh, i.e. 45% premium to IPO price on December 8, 2017**

MAJOR PIPELINE MILESTONES AND PRIORITIES

	PREVIOUS 3 MONTHS	NEXT 12-18 MONTHS
LRRK2	▪ DNL201: Target engagement HV ▪ DNL151: FIH dosing HV P1 study	▪ DNL201 & DNL151: Phase 1 data in HV ▪ Nominate candidate for P1b study in LRRK2 PD patients ▪ **P1b safety and biomarker data in LRRK2 patients**
RIPK1	▪ DNL747: Completed IND-enabling studies	▪ DNL747: Submit CTA and start HV Ph1 study; obtain safety and biomarker data in HV ▪ **DNL747: P1b study in AD and ALS patients; obtain safety and biomarker data**
ATV	▪ Robust and sustained increase in brain exposure ▪ POC in nonhuman primates	
ETV platform		▪ IDS: Data from hTfR mouse model; *in vivo* PK/PD data ▪ **IDS: Establish cell line / manufacturing for clinical supply** ▪ Optimize and select further lead enzymes for multiple programs
Deals	▪ Collaboration with Takeda on 3 named ATV programs	
ATV platform		▪ Optimize existing lead antibodies and select further lead antibodies for multiple programs ▪ **Establish cell line / clinical supply manufacturing for multiple ATV programs** ▪ Expansion of ATV platform technology

OUR PEOPLE

SCIENTISTS AND DRUG DEVELOPERS

137 BASED IN SOUTH SAN FRANCISCO

BOARD OF DIRECTORS

VICKI SATO (CHAIR) | MARC TESSIER-LAVIGNE | DOUG COLE | JAY FLATLEY | ROBERT NELSEN | DAVID SCHENKEIN | RYAN WATTS

HARVARD UNIVERSITY | FLAGSHIP PIONEERING SCIENTIFIC VENTURES FOR LIFE | ARCH Venture Partners | DENALI THERAPEUTICS | Stanford University | illumina | agios

LEADERSHIP

RYAN J. WATTS, PHD – CEO

- Previously built and led Genentech's neuroscience strategy, portfolio and research department
- Led several clinical development programs in neurodegeneration and oncology
- Stanford PhD, University of Utah

ALEXANDER SCHUTH, MD – COO

- Formerly head of Genentech's BD groups for neuroscience and discovery technologies
- Previously Merrill Lynch ECM (London)
- Charite Medical School (Berlin) MD, Wharton MBA

CAROLE HO, MD – CMO

- Formerly VP Early Clinical Development at Genentech
- Previously Medical Director at J&J and clinical neurologist at Stanford
- Cornell Medical School MD, Harvard College

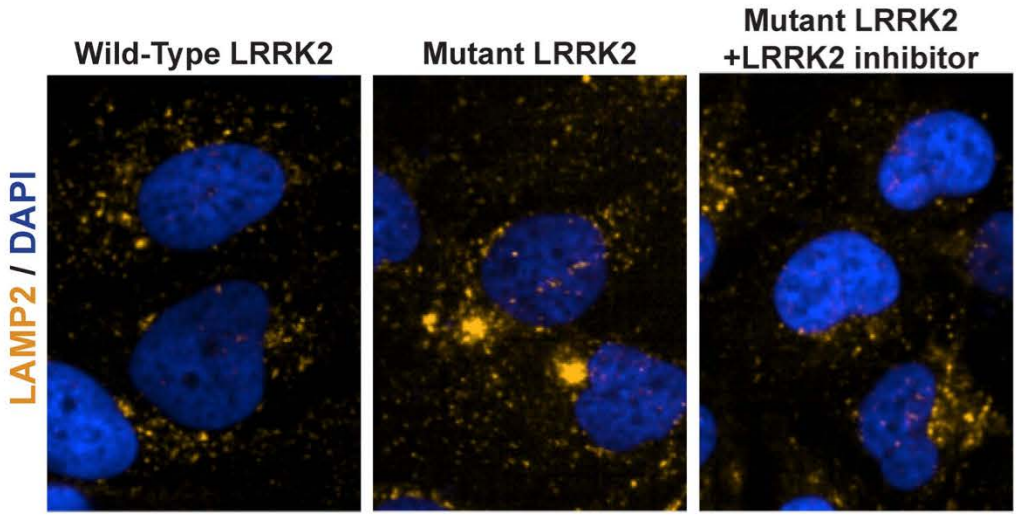
STEVE KROGNES – CFO

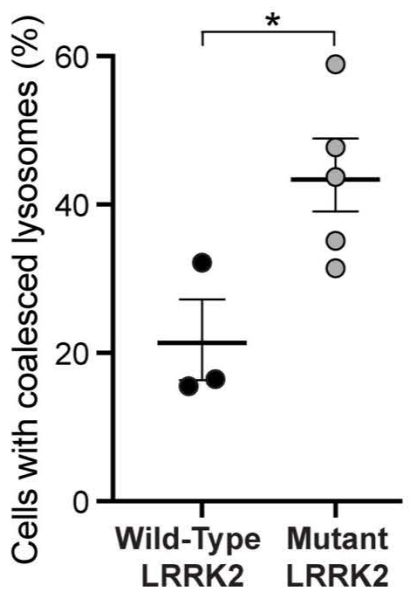
- Formerly CFO Genentech and Head of M&A Roche
- Previously Goldman Sachs and McKinsey
- Harvard Business School MBA, Wharton

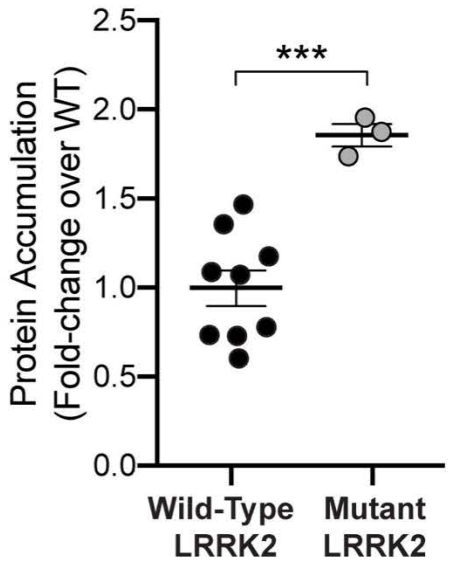

THANK YOU

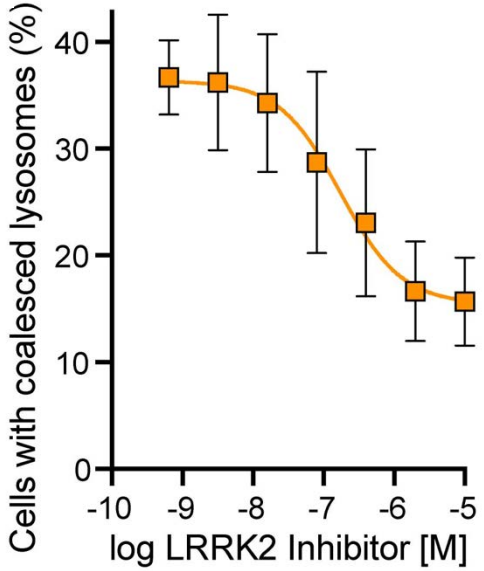
INHIBITION OF LRRK2 BLOCKS LYSOSOMAL DYSFUNCTION

Expression of mutant LRRK2 G2019S results in abnormal lysosomal biology







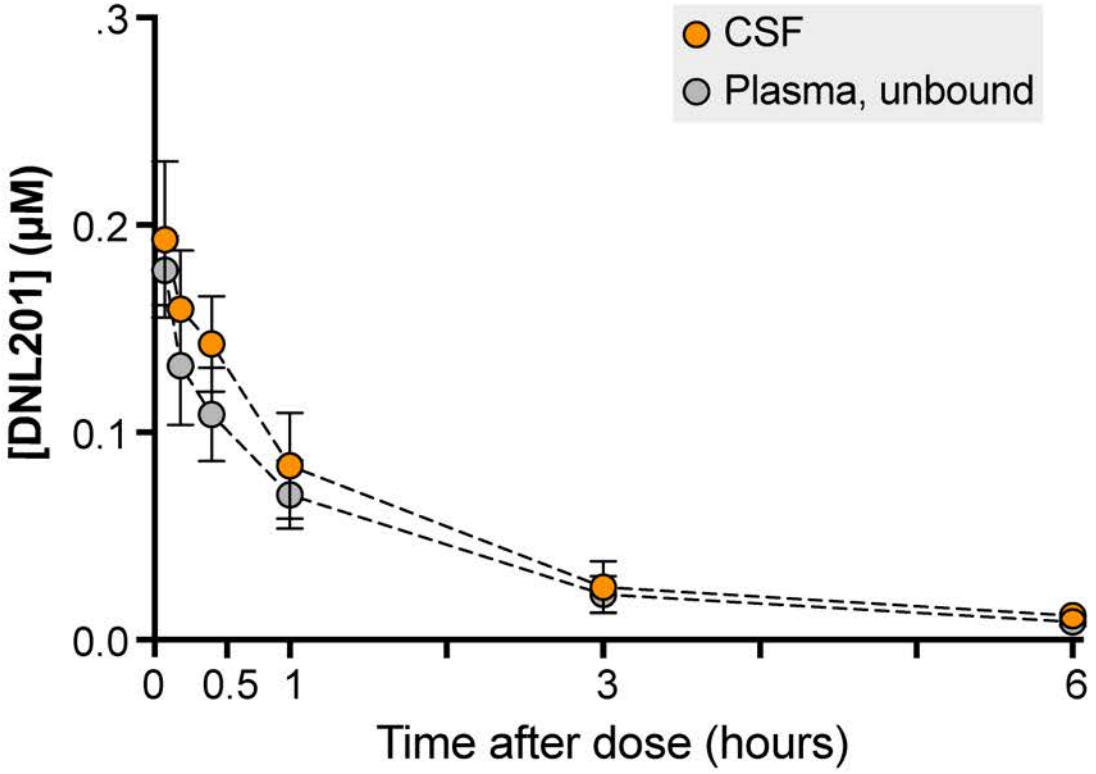


- Mutated LRRK2 (G2019S) results in coalesced, dysfunctional lysosomes (yellow; protein accumulation)
- LRRK2 inhibition with DNL201 can block abnormal lysosomal phenotype

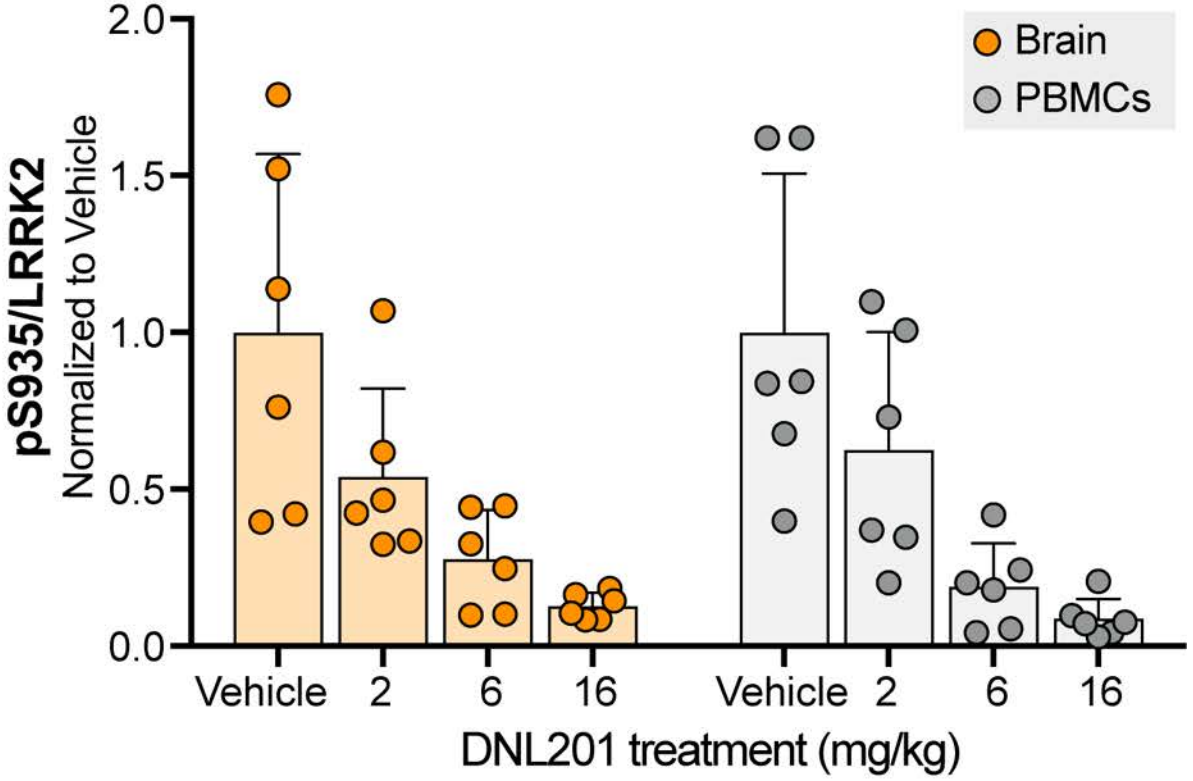
LRRK2 Inhibitor

DNL201 PHARMACOLOGICAL PROPERTIES AND BRAIN EXPOSURE

PK: drug concentration brain (CSF) and blood



PD: equal LRRK2 inhibition in brain and blood

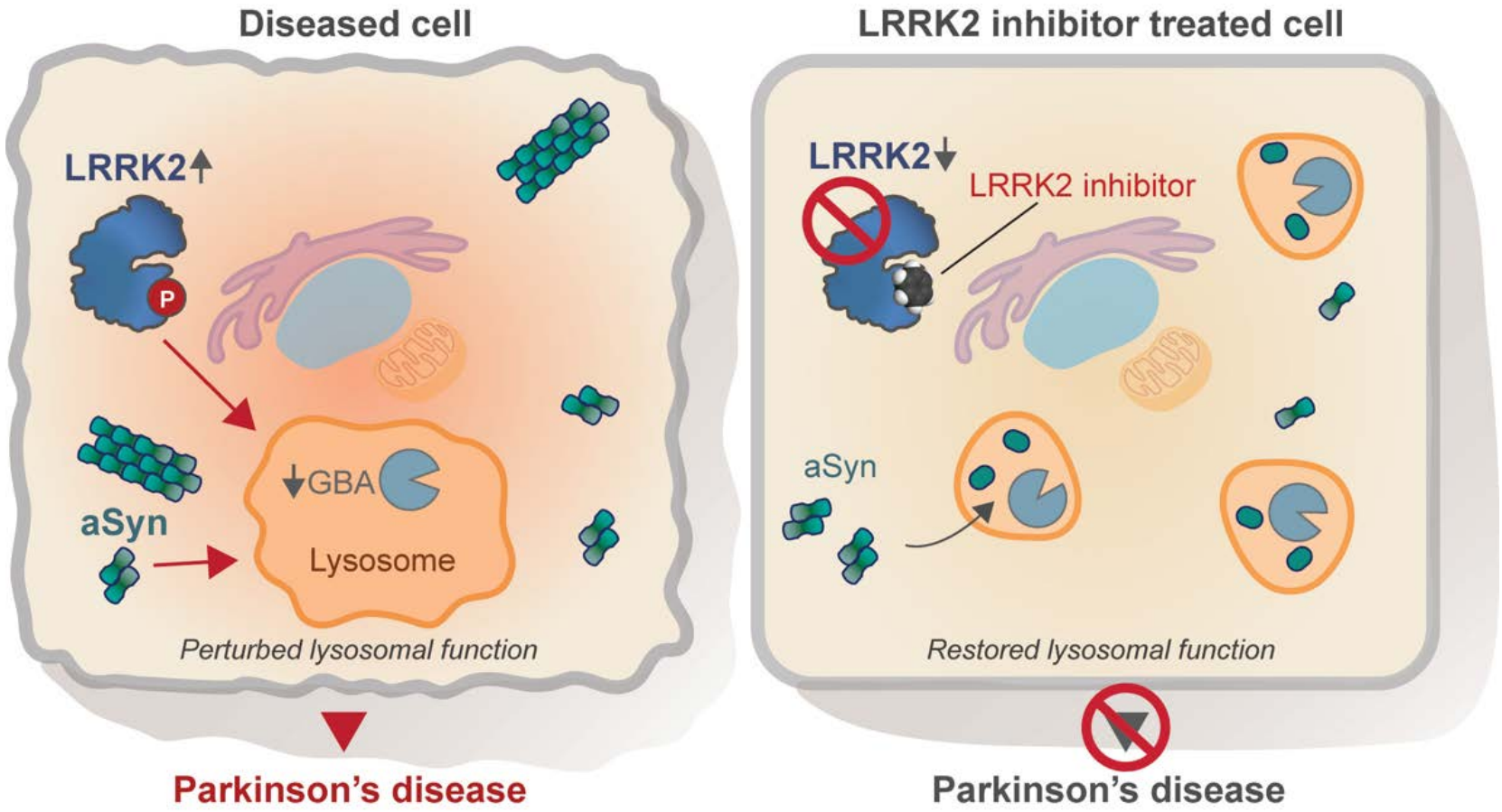


- DNL201 concentrations in monkey plasma (unbound) and CSF demonstrate comparable plasma unbound and CSF exposures
- Comparable pS935 inhibition in PBMCs and brain is observed in monkey 24 hours after the last dose is given

LRRK2 Inhibitor

LRRK2 HYPERACTIVITY DRIVES LYSOSOMAL DYSFUNCTION AND PD

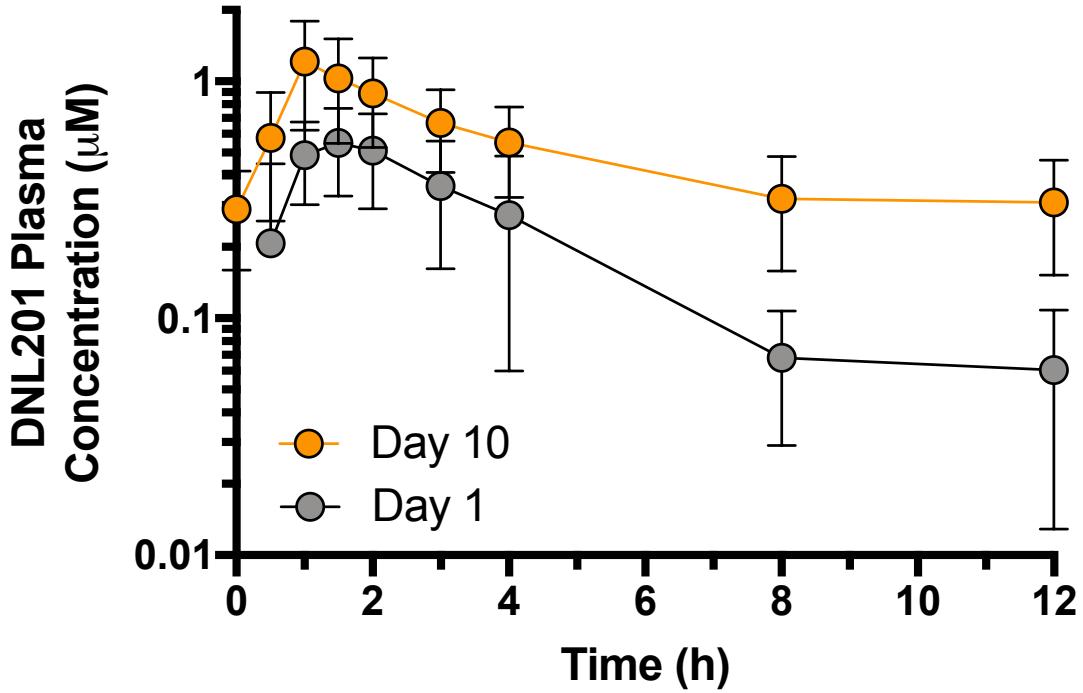
- Increased LRRK2 kinase activity impairs lysosomal function and drives familial PD
- LRRK2 inhibition can restore normal lysosomal function and reduce toxicity in PD models



LRRK2 Inhibitor

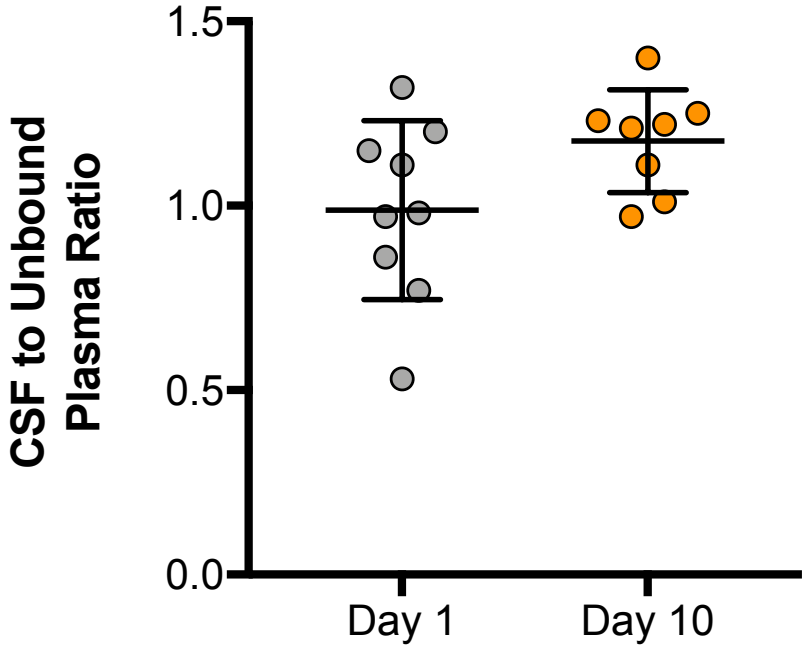
DNL201 PHARMACOKINETIC PROPERTIES AND BRAIN EXPOSURE

PK: drug concentration in blood



- PK profile supports twice daily dosing
- Terminal half life of 14-22 hours
- Low to moderate variability
- Steady state reached by Day 10

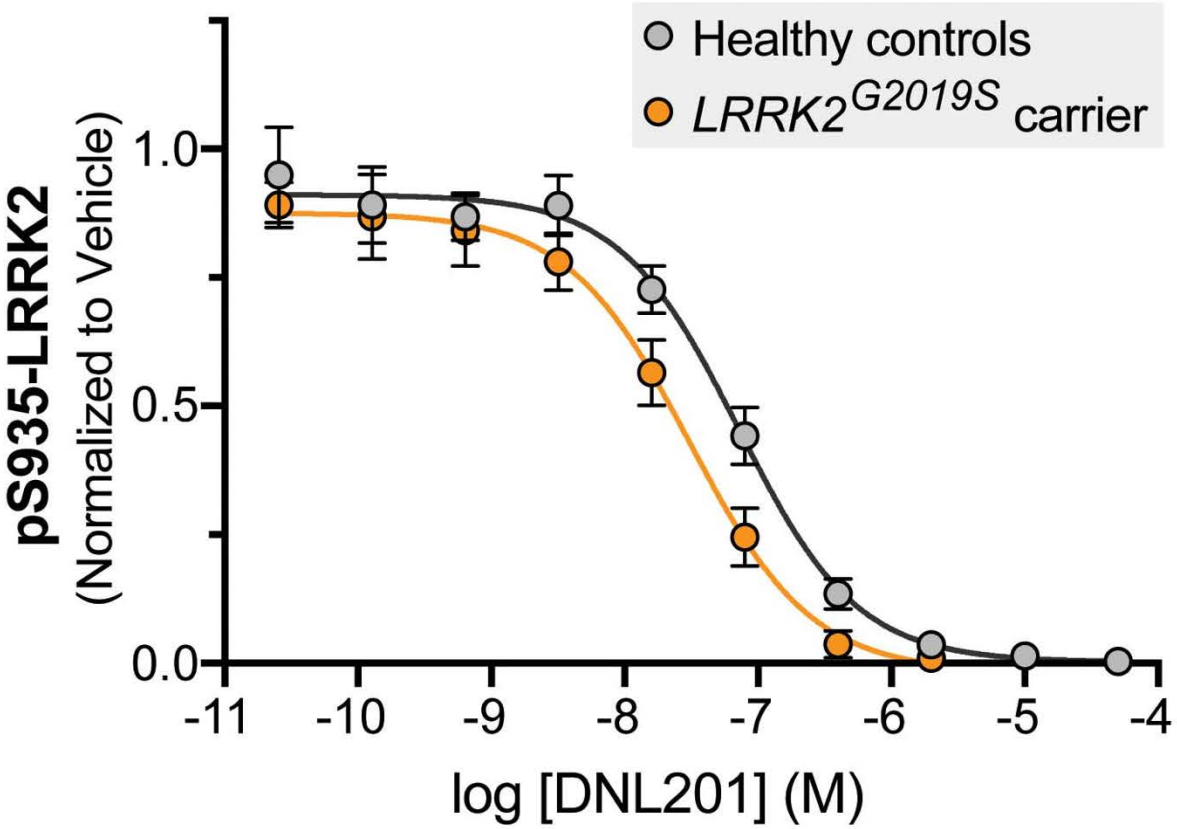
PK: drug concentration in CSF

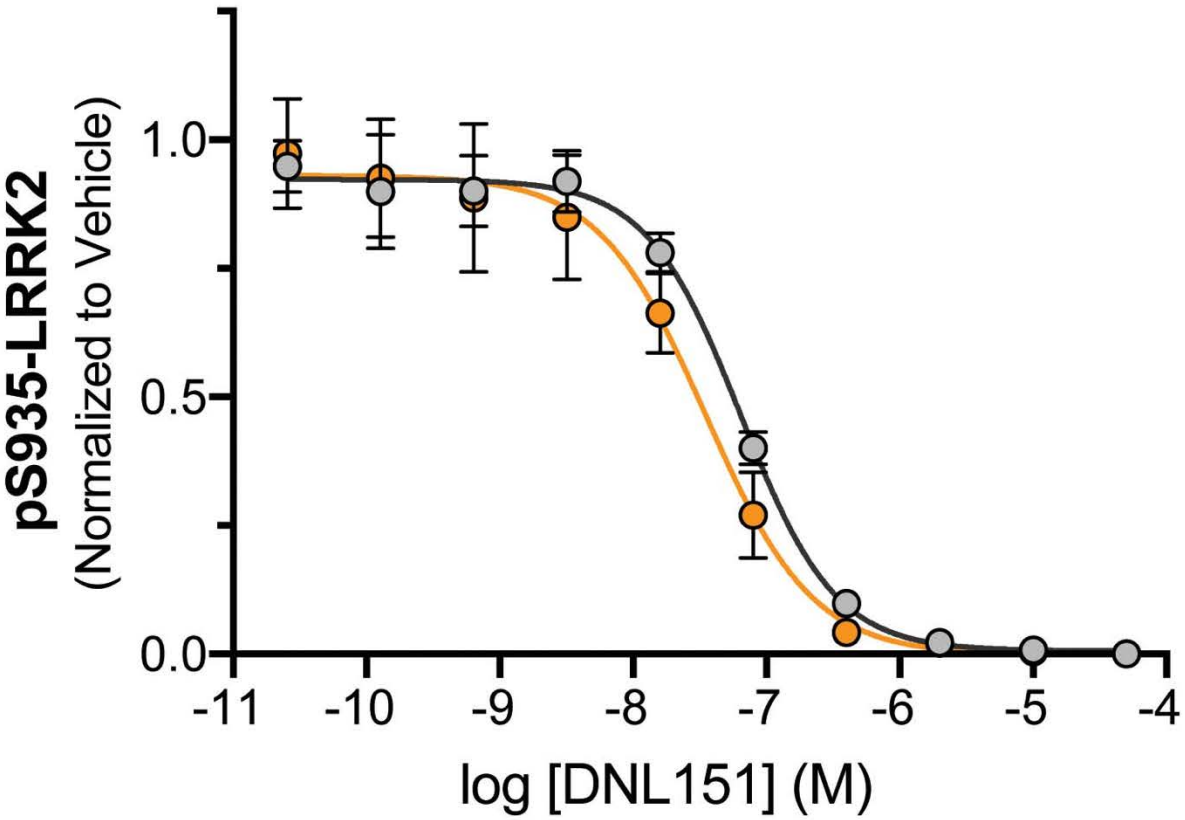


- DNL201 shows a mean CSF to unbound plasma ratio of ~1.0

LRRK2 Inhibitor

INHIBITION OF LRRK2 IN MUTATION CARRIERS



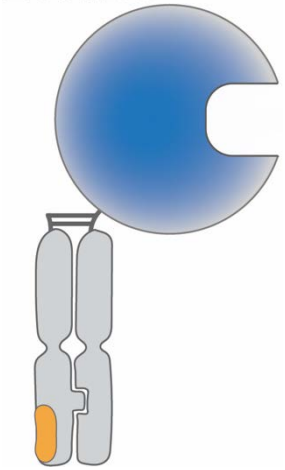


- Both DNL201 and DNL151 robustly inhibit LRRK2 in human mutation carrier blood (*ex vivo*)
- We are actively working with 23andMe to expand our collaboration to include patient recruitment

LRRK2 Inhibitor

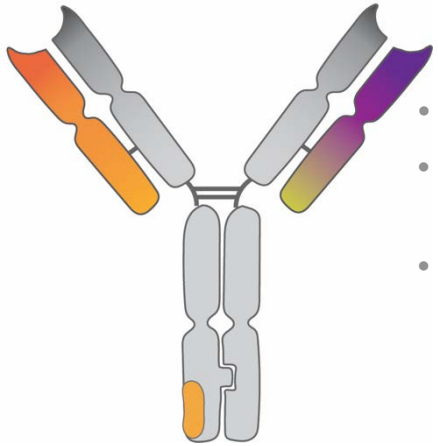
LARGE MOLECULE TARGETS: ATV AND ETV PLATFORM PORTFOLIO

ETV:IDS



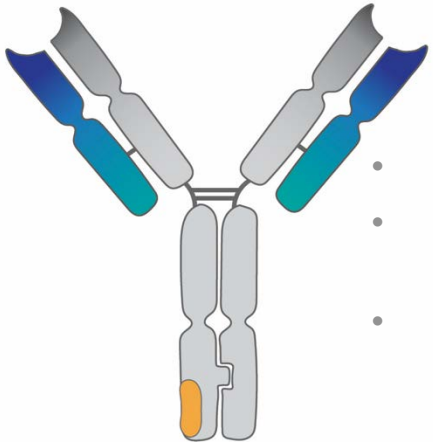
- Indication: **Hunter Syndrome**
- Status: *in vitro* and *in vivo* activity, candidate selections
- IND or CTA filing planned in 2019

ATV:BACE1/Tau



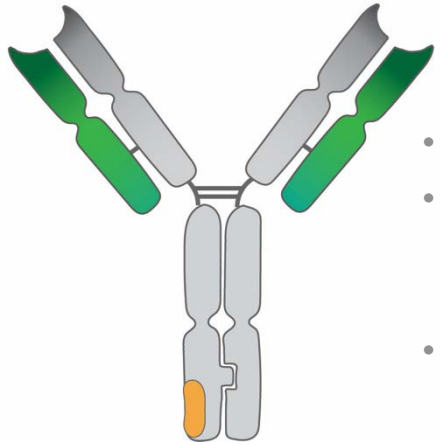
- Indication: **Alzheimer's disease**
- Status: high affinity, humanized leads for BACE1 & Tau
- IND or CTA filing planned in 2020

ATV:aSyn



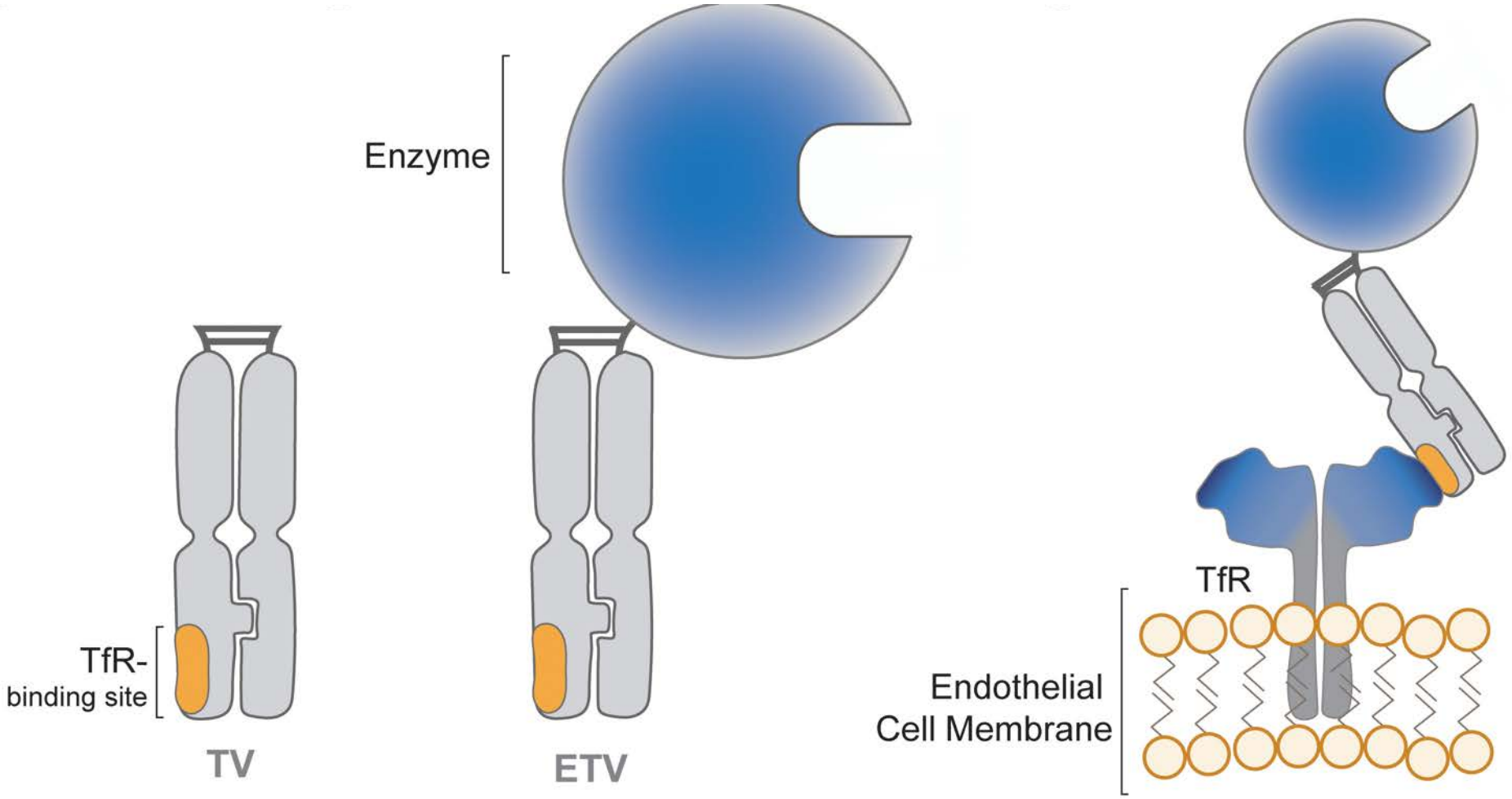
- Indication: **Parkinson's disease**
- Status: multiple lead antibodies identified with robust binding to human CSF derived aSyn
- IND or CTA filing planned in 2020

ATV:TREM2



- Indication: **Alzheimer's disease**
- Status: high affinity candidate antibodies with diverse properties
  - Shedding blockers and agonist antibodies
- IND or CTA filing planned in 2020

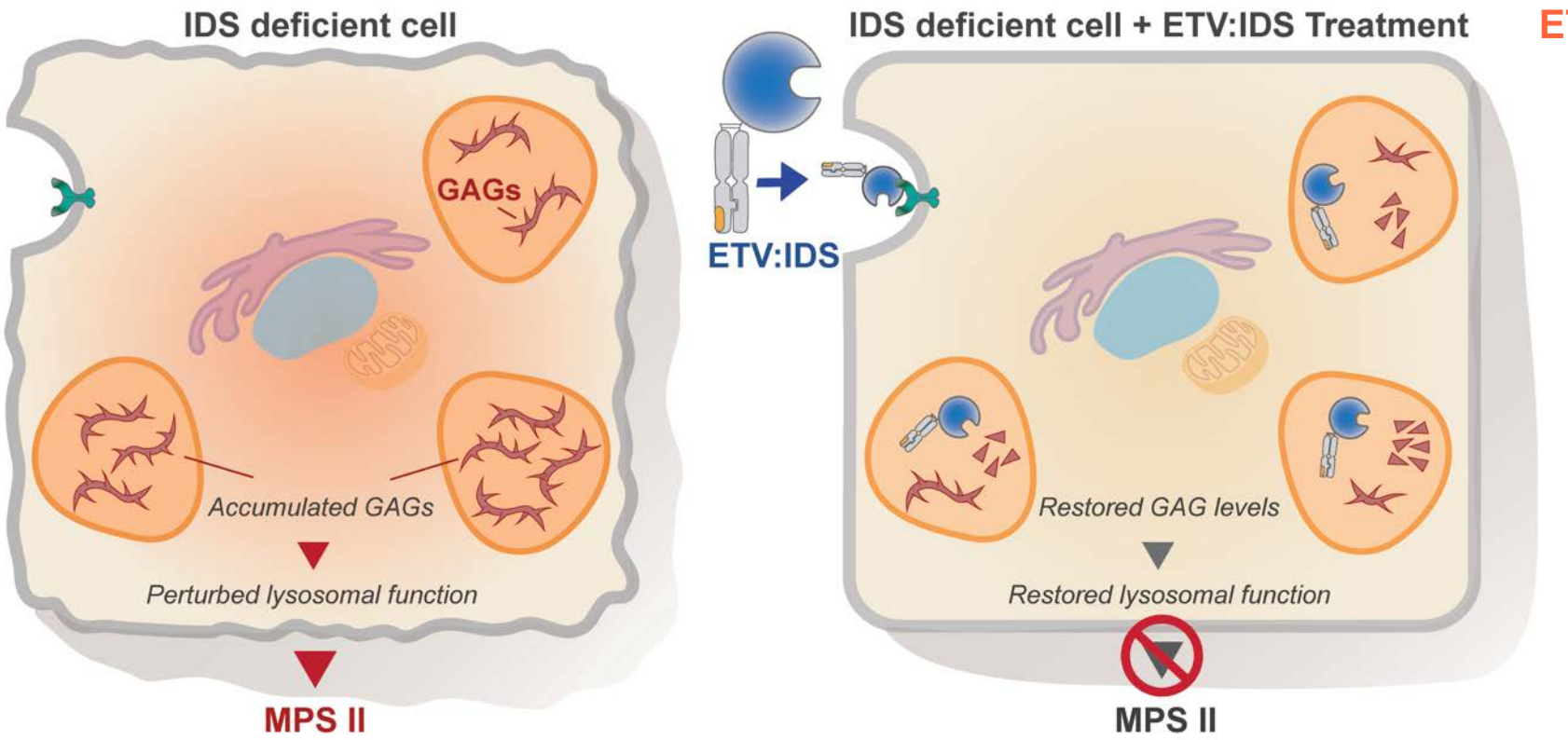
ENZYME TRANSPORT VEHICLE



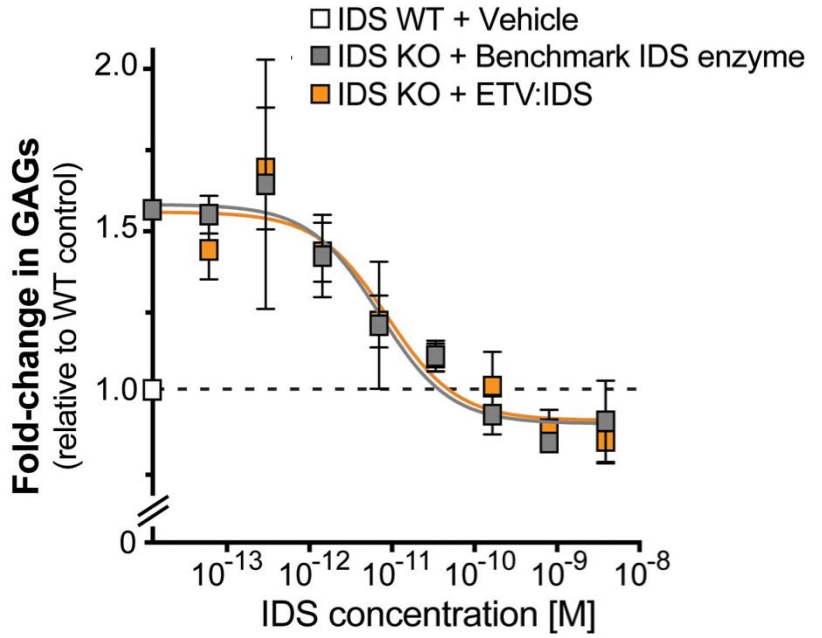
- ETV technology contains BBB receptor (TfR) binding Fc domain fused to an enzyme
- Enables transport of enzymes into the brain through TfR-mediated transcytosis

ETV:IDS

LACK OF LYSOSOMAL ENZYME IDS RESULTS IN MPS II (Hunter Syndrome)



ETV:IDS reduces substrate in IDS KO cells

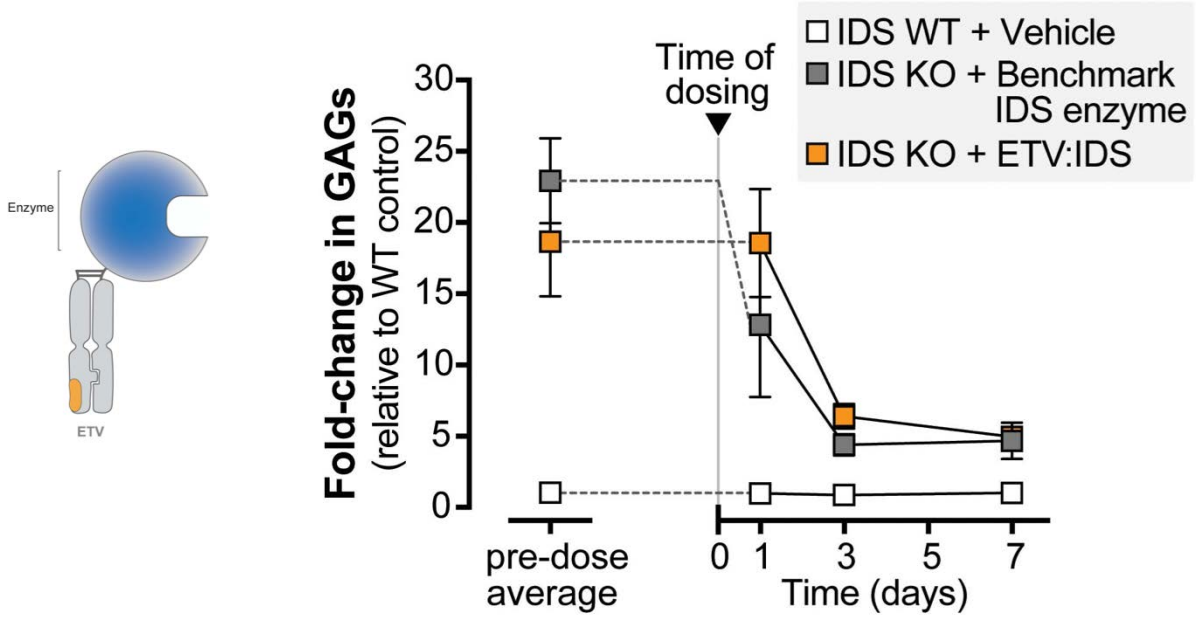


- Treatment with ETV:IDS should promote GAG processing and may rescue neurons from degeneration

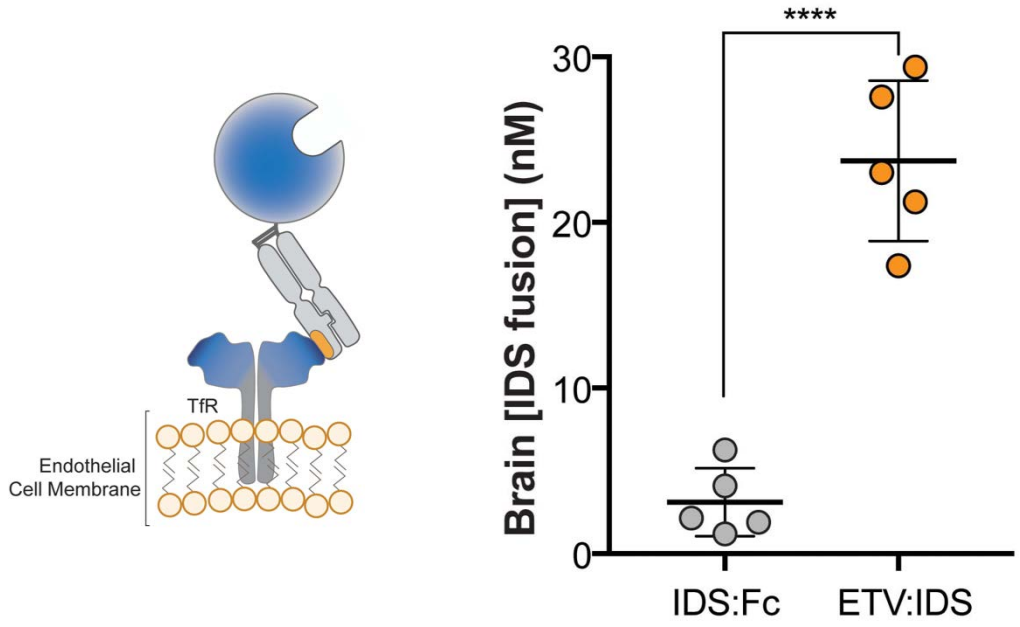
ETV:IDS

ETV:IDS REDUCES SUBSTRATE IN IDS KO MOUSE
ETV:IDS SHOWS ROBUST BRAIN UPTAKE IN HU/MS TFR KI MICE

ETV:IDS reduces substrate in IDS KO mice



ETV:IDS is taken up in TfR$^{hu/ms}$ mouse brain



- IND or CTA filing planned for 2019

ETV:IDS